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Synthesis of Novel Heterocyclic α -Amino Acids

A thesis submitted for the degree of
Doctor of Philosophy in Chemistry

To

The Open University

Milton Keynes

By

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July 2001

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Declaration

I declare that the work presented in this thesis is the result of my own investigations, and where the work of others is cited, it is fully acknowledge. The material embodied in the thesis has not been submitted, nor is currently being submitted for any other degree.

.....

D. J. C.Berthelot

.....

Prof. R.C.F.Jones

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I would like to thank both my supervisors Professor Ray Jones and Dr Jim Iley for their guidance, support and endless encouragement throughout my PhD studies. I am also grateful to Pravin Patel, Graham Geffs and Gordon Howell for their technical support.

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Abstract

This thesis describes the incorporation of heterocycles as part of an α -amino acid side-chain. Two methods were adopted. The first involved the alkylation of a pseudoephedrine glycinamide enolate using haloalkanes. The method was validated by making the naturally occurring amino acid phenylalanine. Subsequently naphthyl-, pyridyl-, biphenyl- and isoxazolyl- groups were successfully incorporated into the amino acid side chain. The enantiomeric excess of the product amino acids was found to be moderate (10-87%) due to poor diastereoselectivity in the key alkylation step. Moreover, the strict experimental conditions required for the alkylation reaction were found to be difficult to reproduce. Attempts to apply this enolate anion strategy to the incorporation of nucleic acid bases utilising an analogous purine electrophile failed, the reaction leading only to elimination.

Thus, amino acids that carry a nucleic acid base in the side chain were synthesised by an alternative method. In this, *N*-(2-iodoethyl)- and *N*-(3-iodopropyl)-pyrimidines and purines underwent stereoselective conjugate radical addition with an optically active oxazolidinone acceptor derived from (R)-*S*-methyleysteine to give *syn*-adducts. Hydrolysis of the oxazolidinone adducts followed by deprotection afforded the desired amino acids carrying pyrimidine- (thymine, uracil) and purine- (adenine, guanine) containing side chains. The enantiomeric excesses, which reflect the diastereoselectivity of the radical addition step, were found to be between 85 and 89%.

Abbreviations

$[\alpha]_D^{20}$	specific rotation (measured with sodium D line, sample at 20°C)
Ac ₂ O	acetic anhydride
AcOH	acetic acid
ACPD	(1 <i>S</i> ,3 <i>R</i>)-1-aminocyclopentane-1,3-dicarboxylic acid
AIBN	2,2'-azobis-(2-methylpropionitrile)
AMPA	(<i>S</i>)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid
Anisyl	methoxyphenyl
aq.	aqueous
b.p.	boiling point
Boc	<i>N</i> - <i>tert</i> -butoxycarbonyl
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
BzCl	benzoyl chloride
cat.	catalyst
Cbz	benzyloxycarbonyl
CNS	central nervous system
c.	concentration
COSY	two-dimensional correlated spectroscopy
d.e.	diastereoisomeric excess
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine

DMB	dimethoxybenzyl
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
e.e.	enantiomeric excess
EAA	excitatory amino acid
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
equiv.	molar equivalents
FAB	Fast atom bombardment
h	hours
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole hydrate
Hz	Hertz
i-GluRs	ionotropic glutamate receptors
IR	infrared
LDA	lithium diisopropylamide
m.p.	melting point
m/z	mass to charge ratio
m-GluRs	metabotropic glutamate receptors
MH	molecular ion isotope peak determined by CI or electrospray mass spectrometry
MHz	megahertz
min	minutes
mmol	millimoles
MNH ₄ ⁺	molecular ion peak determined by ammonia chemical ionisation mass spectrometry
mRNA	messenger ribonucleic acid

MTPA-Cl	2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride
NAD	nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NBS	N-bromosuccinimide
NMDA	N-methyl-D-aspartic acid
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
Oxone	potassium peroxymonosulfate
Pivaldehyde	2,2-dimethylpropanal
Pivalyl	2,2-dimethylpropanoyl
PMB	4-methoxybenzyl
PNA	peptide nucleic acid
PNP	<i>para</i> -nitrophenyl
Pyr	pyridine
RNA	ribonucleic acid
RT	room temperature
SAR	<i>structure activity relationship</i>
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane or trimethylsilyl
TMSCN	trimethylsilyl cyanide
TRH	thyrotropin releasing hormone
TSH	thyrotropin stimulating hormone
v/v	proportions of two components expressed as a ratio of their volumes
Z	carbobenzyloxy

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CHAPTER 1

INTRODUCTION

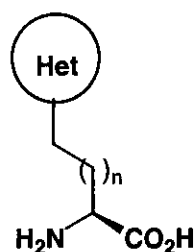
1.0 Introduction

The synthesis of non-proteinogenic α -amino acids in enantiomerically pure form is an important goal because of their increasing role in biology and chemistry¹. They are present in natural and pharmacologically active compounds. The presence of these amino acids as residues in peptides can render such peptides resistant to enzymatic degradation. These non-proteinogenic amino acid residues also have conformation-inducing properties in designed peptides and proteins². According to the substitution pattern at the α -position, they can be classified as mono- and dialkylated α -amino acids. α -Substituents include allyl, aryl, vinyl and heterocyclic groups, the latter class being particularly attractive because of the hydrogen bonding possibilities that can create a lot of diversity in biological activity.

This introduction will therefore outline some background regarding the biological significance of certain classes of heterocyclic amino acids. Further, to give a wider perspective to the synthetic methodologies that we employed to assemble our unusual amino acids, we will also review briefly the more important strategies available in the literature to date. Except where the methodology or examples are directly relevant to the work in this thesis, we have limited the discussion to heterocyclic amino acids.

1.1 Objectives

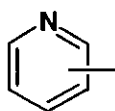
The goal of this work was the synthesis of novel nitrogen-containing heterocyclic amino acids, of the general structure **1.1** shown below, that can be incorporated into important biologically active targets.



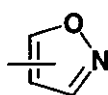
1.1

At the outset, we decided to use and develop existing synthetic methodologies rather than develop a new methodology. One requirement we made of the chosen methodology was that it should be stereoselective, in contrast to the less challenging strategy that employs an already existing stereocentre in the amino acid backbone. A further requirement of this work was to choose a methodology that would permit a variation of the distance between the heterocycle and the amino acid backbone.

We decided to focus our attention towards nitrogen- and oxygen- containing heterocycles. Amongst the simplest heterocyclic cores are the pyridyl, **1.2**, and isoxazolyl, **1.3**, rings; synthetically, these represent a simple challenge, as no protecting group would be required.

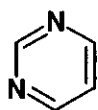


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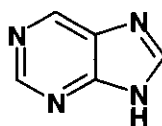


1.3

Moreover, many of the simpler precursors are commercially available. Having assessed the viability of the route using these, we could then extend the method to other, perhaps more interesting, heterocycles such as those derived from pyrimidine, **1.4**, and purine, **1.5**.



1.4

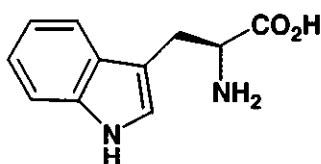


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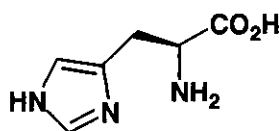
The biological relevance of those chosen targets is discussed in the next section.

1.2 Heterocyclic α -amino acids

The twenty main naturally occurring α -amino acids are the fundamental building blocks of peptides, proteins and other natural products. Consequently, they fulfil fundamentally important roles in biology and chemistry such as structural (e.g. muscle), recognition (e.g. receptors), communication (e.g. hormones, neurotransmitters), transformation (e.g. enzymes) and regulation (insulin)³. Amongst these twenty natural amino acids, histidine and tryptophan are the only two that bear a heterocyclic side chain.



(S)-Tryptophan



(S)-Histidine

Tryptophan is important as the major precursor of the nicotinamide nucleotide coenzymes, NAD and NADP, and in the central nervous system as the precursor of the transmitter serotonin (5-hydroxytryptamine). The indole nucleus of tryptophan is also present in many fungal toxic peptides such as phalloidin and amanitin⁴.

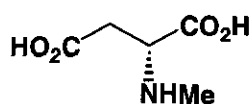
The imidazole group in histidine is essential for the biological activity of a variety of enzymes, including the serine and cysteine proteases⁵. In the active centre, the histidine residue may serve as both donor and acceptor in hydrogen-bonding interactions, and it can also promote proton transfer by a general acid-base catalysis. Moreover, the imidazolyl nitrogen atoms are making histidine an efficient nucleophile both for acyl transfer reactions and for coordination to metals. Modification of the histidine residue in peptides can produce dramatic changes in biological activity (see section 2.2).

In the following sections, the focus will be first on the role of heterocyclic amino acids as natural products, then on the introduction of such heterocyclic amino acids into peptides, and finally we will discuss briefly the recent advances concerning the manipulation of heterocyclic amino acids in relation to DNA.

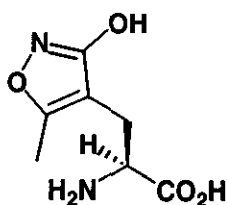
1.2.1 Heterocyclic amino acids as natural products

The synthesis of natural products is one of the most important and challenging areas in organic chemistry. Many natural products contain amino acids.

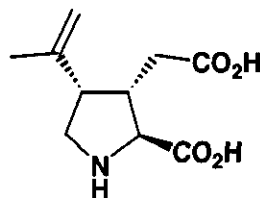
For example, excitatory amino acids (EAA) are known to mediate synaptic excitation, and therefore nerve signal transmission, by binding to EAA receptors⁶. EAA receptors can be divided into two main classes, namely, the ionotropic glutamate receptors containing the AMPA ((S)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid), KA (kainic acid) and NMDA (N-methyl-D-aspartic acid) receptors, and the metabotropic glutamate receptors containing ACPD (1-aminocyclopentane-1,3-dicarboxylic acid), group I, group II and group III receptors.



NMDA

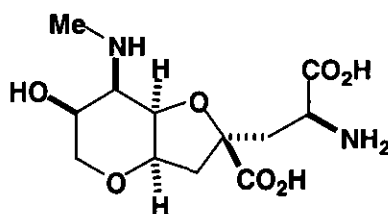


(S)-AMPA



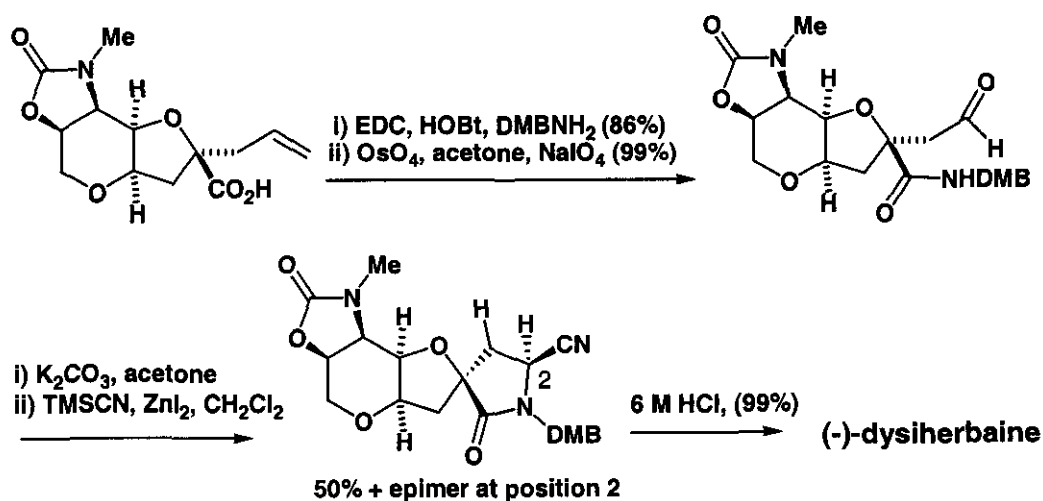
Kainic acid

All these receptors are potential targets for therapeutic intervention in a number of diseases, such as Alzheimers and schizophrenia⁷. Consequently, compounds capable of activation of excitatory amino acid receptors (agonists) have potential as drugs for these disorders. One recent example displaying activity at iGlu-Rs (agonist for non-NMDA glutamate-type receptors), is the natural amino acid dysiherbaine **1.6**, isolated from the Micronesian marine sponge *Dysidea herbacea* by Sakai and co-workers in 1997⁸.



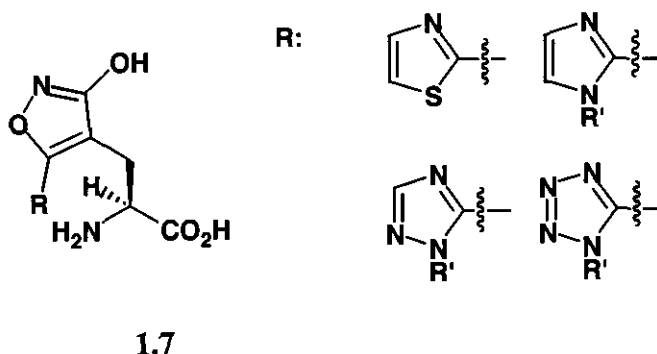
1.6

A synthesis of this challenging natural product target which contains six chiral centres, has recently appeared (Scheme 1.1)⁹. In the penultimate step, the centre that becomes the chiral centre at the α -position in the amino acid is generated as a 1:1 mixture of epimers of separable nitriles.



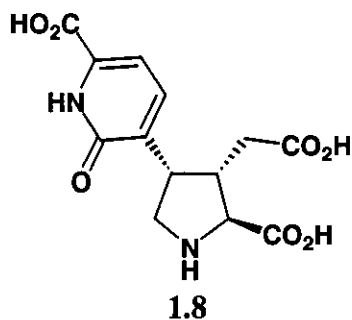
Scheme 1.1

The AMPA receptor is selectively activated by (*S*)-AMPA, and the synthesis of heteroarylalanine analogues of AMPA **1.7** that could serve as receptor ligands has been accomplished¹⁰.

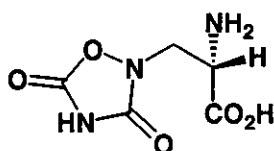


Although these (*S*)-AMPA analogues have shown full agonist activity, no simple SAR correlations were found. Further development of amino acids containing isoxazole, aromatic or heteroaromatic rings is therefore still necessary to provide potential candidates as AMPA receptor agonists.

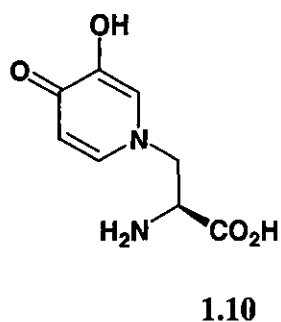
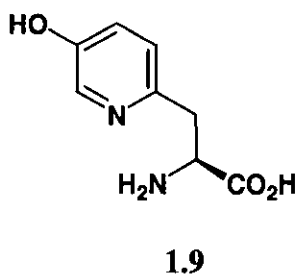
The synthesis of kainic acid analogues is also an intense area of research and it has been suggested that they may have a useful role in the treatment of epilepsy¹¹. Many analogues of the natural product acromelic acid **1.8** have shown some activity¹².

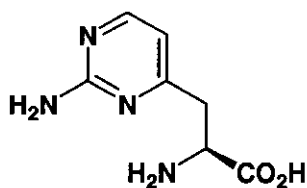


One further naturally occurring heterocyclic excitatory amino acid that has received a lot of attention is quisqualic acid. This activates metabotropic glutamate Group I receptor⁶.

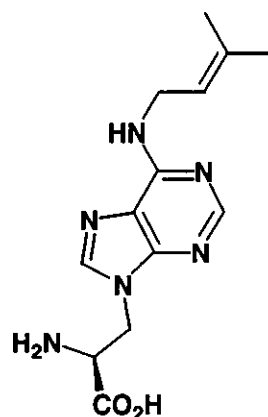


Apart from compounds that act at glutamate receptors, other natural amino acids such as the pyridyl derivative azatyrosine **1.9** and the dihydropyridyl derivatide mimosine **1.10** have been observed to display antibiotic, wool growth hormone and pollen growth inhibition activity¹³. Lathyrine **1.11**, a pyrimidine-containing α -amino acid, and discadenine **1.12** (isolated from *Dictyostelium discoideum*¹⁴), a purine-containing α -amino acid, also display biological activity.





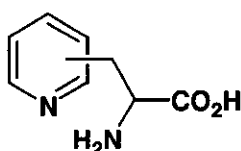
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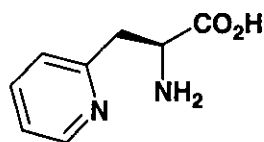
1.2.2 Heterocyclic α -amino acids as natural amino acid replacements

We have seen that natural heterocyclic α -amino acids, as well as synthetic analogues, have biological activity in their own right. However they can also induce biological activity when incorporated into natural or designed peptides. For example, pyridyl amino acids **1.13** serve as a replacement of histidine and phenylalanine in numerous biologically active compounds. Indeed, it is well known that pyridylalanines and substituted analogues exhibit diverse pharmacological effects when introduced into biological systems¹⁵.

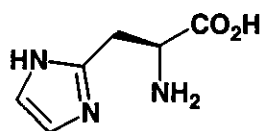


1.13

More precisely, in angiotensin II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-) the replacement of the histidyl residue by basic, neutral, acidic, and aromatic residues gave analogues with low biological activity. Therefore, the structural features of histidine, namely the electron rich aromatic ring and the two heterocyclic nitrogens was studied in more detail¹⁶. Replacement of histidine by 2-(pyridyl)-(*S*)-alanine **1.14** and 2-(imidazolyl)-(*S*)-alanine **1.15** revealed that the pyrrolic NH is necessary for the interaction of angiotensin II with its receptor, the pyridine nitrogen N9 playing a minor role.



1.14



1.15

1.2.3 Heterocyclic α -amino acids and DNA

The most important molecular recognition event in Nature is the base-pairing of nucleic acids, which guarantees the storage, transfer and expression of genetic information.

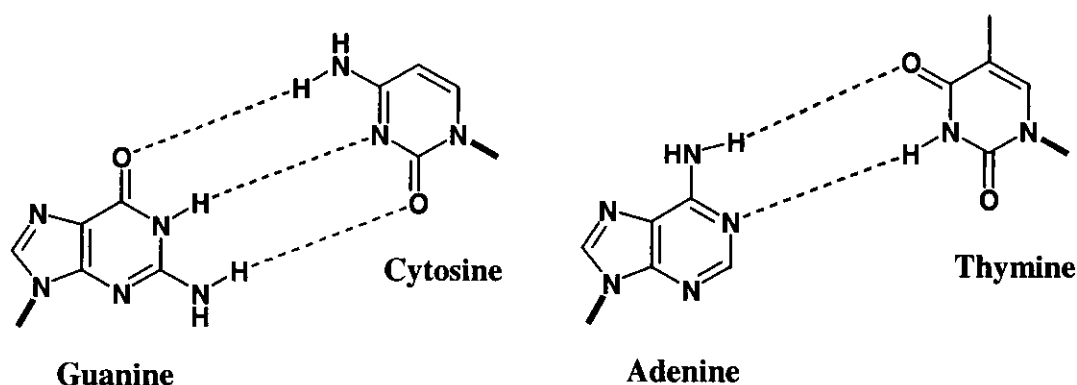
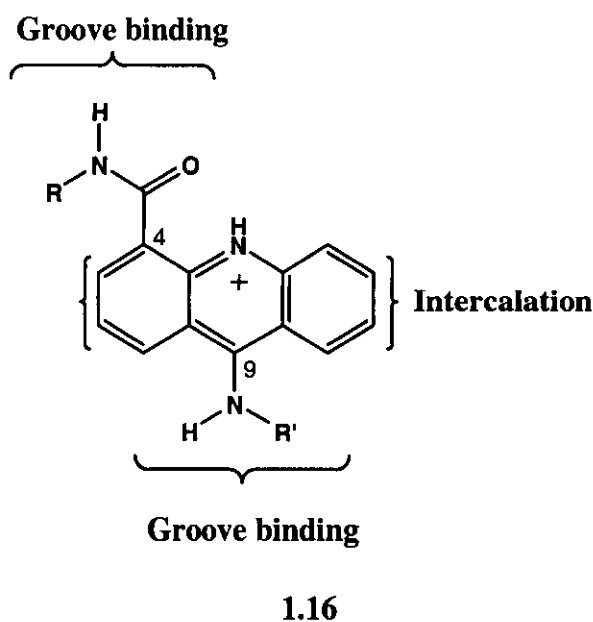


Figure 1.1/Nucleobase recognition by Watson-Crick hydrogen bonding

Highly specific recognition is a result of specific base-pairing between the purine and pyrimidine nucleobases, guanine with cytosine and adenine with thymine (Figure 1.1). These interactions between the nucleic acid bases are responsible for the helical structure of DNA. One way to disrupt this helical structure and the base stacking is to introduce intercalating agents that could intercalate between the nucleic acid bases and interact with the strands of DNA. Another way is to introduce oligonucleotide derivatives which mimic the DNA structure. Finally, a more recent approach that has led to a new and rapidly expanding field of research, namely peptide nucleic acids (PNA), will be treated.

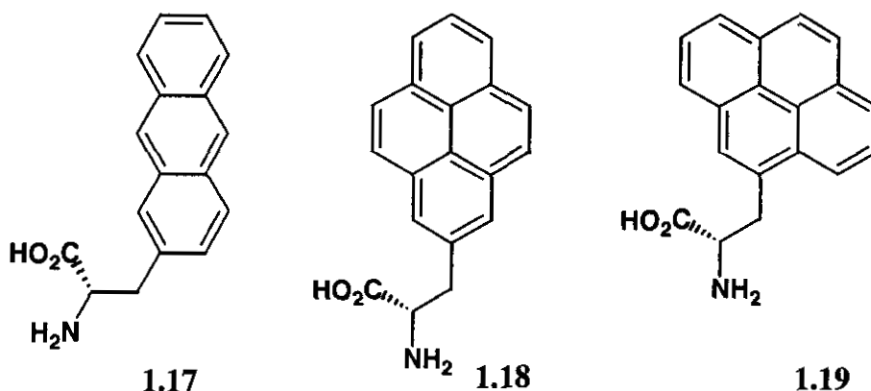
1.2.3.1 Intercalating agents

The primary mode of noncovalent binding of small molecules to DNA and RNA is intercalation and groove binding. Intercalators are molecules that bind to DNA by insertion of an aromatic moiety between the stacked base pairs of double helical DNA. 9-Anilinoacridine-4-carboxamides **1.16**, for example, have shown binding to DNA¹⁷. In the intercalation complex, acridine substituents at the 4- and 9- positions are located in the major and minor grooves with the acridine chromophore sandwiched between base pairs. These compounds allow for base-specific groove binding by the substituents to occur. The ability of intercalators to direct functionality into both the major and minor grooves of nucleic acids makes them good candidates for selective ligands able to provide molecular recognition. In particular, acridines have been shown to be potent inhibitors of the cancer chemotherapy target topoisomerase II¹⁸.



Interestingly, several non-natural amino acids carrying large aromatic groups such as 2-anthrylalanine **1.17**, 2-pyrenylalanine **1.18** and 1-pyrenylalanine **1.19** have been

successfully incorporated into proteins *via* the ribosomal system¹⁹. It has been shown that success in the incorporation depends on the amino-acid used together with recognition by the ribosomal A-site²⁰.



The incorporation of these amino acids could be translated into conformational changes in the protein, enzymes or binding site. One can well imagine designing proteins incorporating amino acids containing large side chains in order to target particular functions or genetic disorders at the desired site.

1.2.3.2 Antisense oligonucleotides

Zamecnick and Stephenson were the first to propose, in 1978, the use of synthetic oligonucleotides for therapeutic purposes²¹ in the inhibition of a virus in a cell culture. The inhibition is based on the specific Watson-Crick base pairing between the heterocyclic bases of the antisense oligonucleotide and of the viral nucleic acid. In order to meet these inhibition requirements, it is necessary for normal oligonucleotides to be chemically modified. We briefly describe below such modifications.

Backbone modifications

DNA structure can be modified at the phosphate backbone level. Phosphorothioate oligonucleotides (Figure 1.2) are those in which one (or more) oxygen atom has been replaced by sulfur and selenium²².

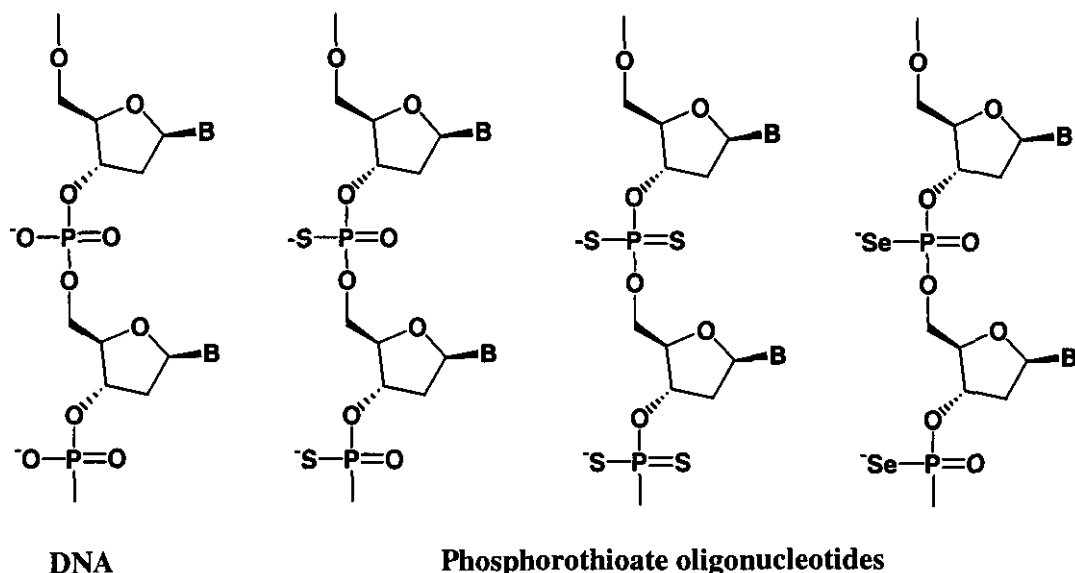


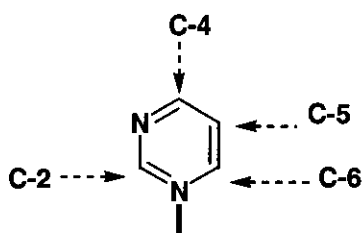
Figure 1.2 Replacement of oxygen atoms in the phosphate backbone of DNA

Indeed, this modification made the oligonucleotides more stable towards degradation by enzymes (nucleases). However, it was found that the binding affinity to mRNA was poor.

Base modifications

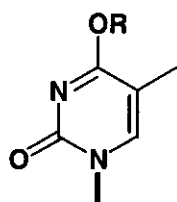
To increase binding affinity and specificity to a complementary nucleic acid sequence, oligonucleotides can also be modified by incorporating 'unnatural' heterocyclic bases. Most of the reported modifications have concentrated on analogues of the purines and pyrimidines that are the principal bases of nucleic acid.

There are four principal sites for modification of the pyrimidine ring: C-2, C-4, C-5 and C-6, 1.20.

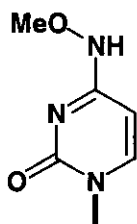


1.20

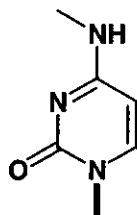
Modifications at C-2 interfere with the hydrogen bonding that is essential for complementary base pairing, and these are therefore unfavourable. Modifications at C-4 include *O*4-alkylthymine **1.21**, *N*4-methoxycytosine **1.22**, *N*4-methylcytosine **1.23**, and pyridopyrimidine **1.24**. The latter modification, **1.24** (which also involves C-5 modification), resulted in a stabilised duplex due to stronger hydrogen bonding than the natural cytosine²³.



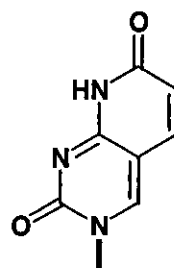
1.21



1.22

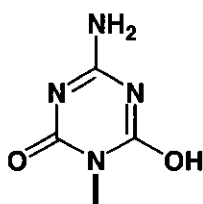


1.23

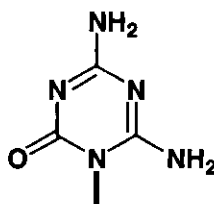


1.24

Modifications at C-6 showed that 6-substituted 5-azacytosines, such as 6-hydroxy- **1.25** and 6-amino-5-azacytosines **1.26** could serve as 'universal' bases in that they hydrogen bond with guanine, thymine and uracil with equal efficiency.



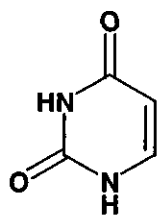
1.25



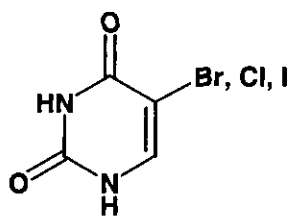
1.26

Uracil **1.27**, a pyrimidine base found in RNA that can hydrogen bond with adenine, has also been the subject of modification. In particular, derivatives **1.28** can also be obtained having a halogen atom at the C-5 position. Oligomers containing these halogenated uracil

derivatives have been shown to form a more stable duplex than the oligomers containing uracil²⁴.

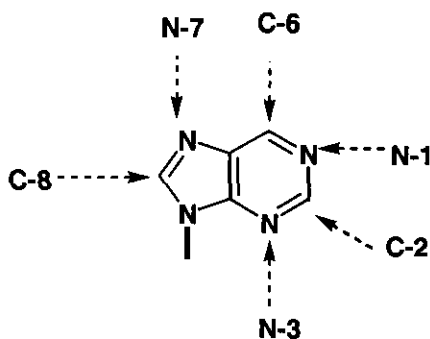


1.27



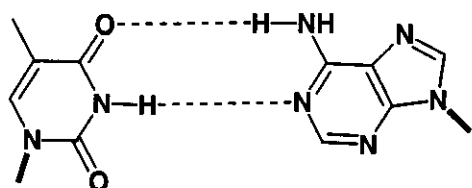
1.28

The main problem with the above modifications is their lack of specificity. This has prevented them from being used in antisense (mRNA targeting) studies.

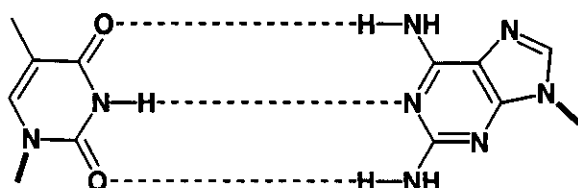


1.29

Modification of the purine moiety **1.29** has produced analogues that are able to form a more stable duplex than their natural counterparts. As an example, incorporation of the 2-aminoadenine **1.30** into oligonucleotides resulted not only in enhanced binding to DNA but also in more specific base pairing *via* the additional H-bond that is formed between the 2-amino group of **1.30** and the 2-oxo group of thymine.

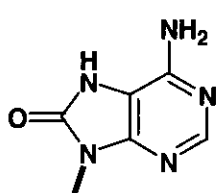


Thymine/Adenine

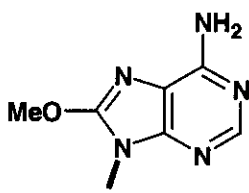


Thymine/2-aminoadenine (1.30)

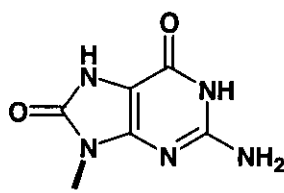
In addition, C-8 modification has provided analogues such as 8-hydroxyadenine **1.31**, 8-methoxyadenine **1.32**, 8-hydroxyguanine **1.33**, and 8-methoxyguanine, **1.34** that possess an increased resistance to enzymes that cleave nucleic acids at phosphodiester bonds²⁵ (nucleases).



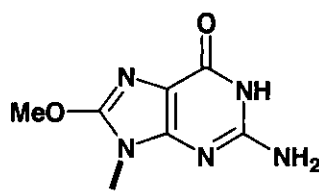
1.31



1.32



1.33



1.34

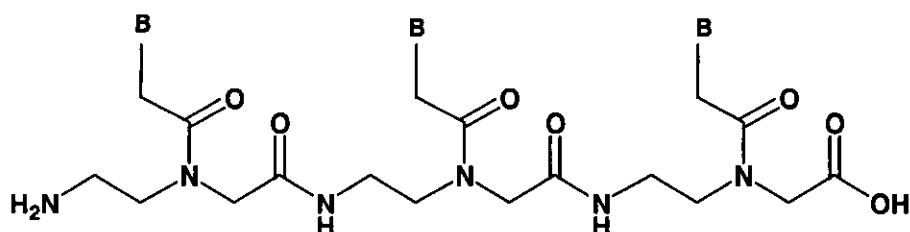
1.2.3.3 Peptide nucleic acid technology

Peptide nucleic acids (PNA) have emerged as a new class of therapeutic agents, designed to inhibit expression of genetic information both as antisense (mRNA targeting) and antigene (DNA targeting) agents. Peptide nucleic acids are being developed to target a particular gene responsible for a genetic defect. Preventing its expression, by interfering with the transcription of a particular sequence, is a much more efficient way of intervening than targeting the genetically defective protein itself.

In order to be ideal therapeutic agents, small oligonucleotide sequences must fulfil at least three fundamental requirements: first, they must bind to target mRNA or DNA according to Watson-Crick base pairing; second, they must be sufficiently robust both inside and

outside the cell environment; and third, they must be able to reach the site of action, just as for any other drug. Natural oligonucleotides themselves have a high affinity for DNA as they bind to DNA *via* Watson Crick base pairing, but they are easily degraded by cellular enzymes. Consequently, they are unsuitable as therapeutic agents. It is therefore necessary to introduce chemical modification for the purpose of intact delivery to the site of action.

The group of Nielsen in the early 1990's reported an entirely different approach towards improving binding affinity to complementary nucleic acid, increasing biological stability, and improving cellular uptake. PNA represents a very dramatic deviation from the natural DNA structure since the entire phosphodiester backbone has been replaced by a pseudopeptide backbone. In this approach, the sugar-phosphate backbone is replaced by an N-(2-aminoethyl)glycine-based polyamide structure **1.35**, in which each subunit incorporates one of the naturally occurring nucleic acid bases attached to the polyamide backbone *via* a modified acetyl group. From a chemical point of view, PNA is a hybrid between an oligonucleotide (nucleobases) and a protein (backbone) and therefore shows properties from both categories.



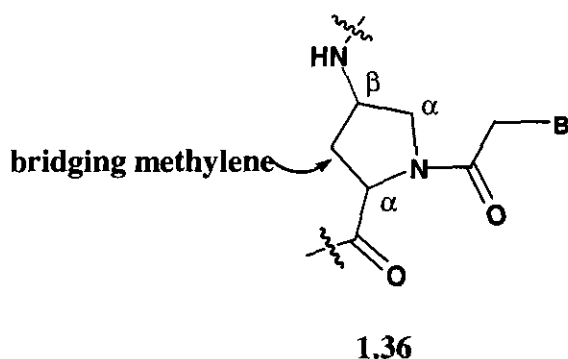
1.35

Nielsen discovered that these PNAs bind with higher affinity to complementary nucleic acids than their natural counterparts and obey the Watson-Crick base pairing rules. An advantage of PNAs over oligonucleotides is that the polyamide backbone is not recognised by either nucleases or proteases and is therefore not cleaved. However a major limitation of PNAs from the perspective of their use as therapeutic agents is their poor solubility in aqueous medium. In addition, being achiral, they bind to complementary DNA in both parallel (PNA/5'DNA) and antiparallel (PNA/3'DNA) modes. In an attempt to impart

discrimination between parallel and antiparallel modes of binding, chirality was introduced into PNA molecules either by linking amino acids²⁶, peptides or oligonucleotides at the terminus or by incorporation of chiral amino acids in place of glycine into the PNA backbone. Of course, symmetry can also be introduced into PNA through incorporation of cyclic amino acids into the PNA backbone.

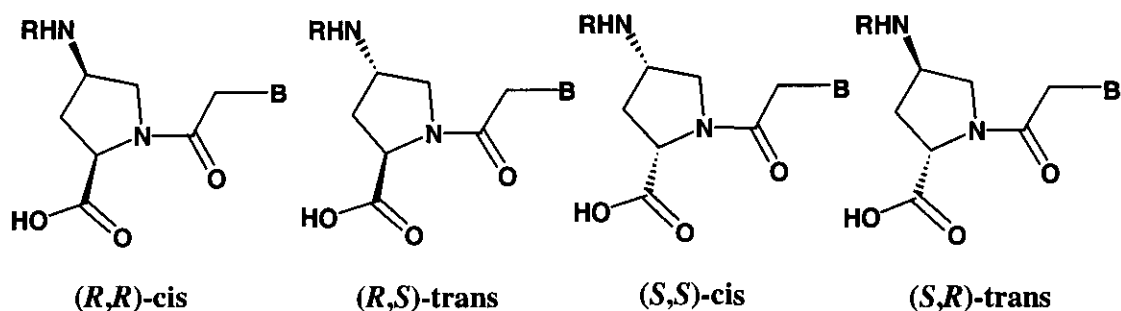
Incorporation of cyclic amino acids into the PNA backbone

Kumar and Ganesh²⁷ have employed PNA monomers containing stereospecific chemical modifications. They envisaged introducing chirality into the backbone by synthesising the modified proline unit **1.36**.



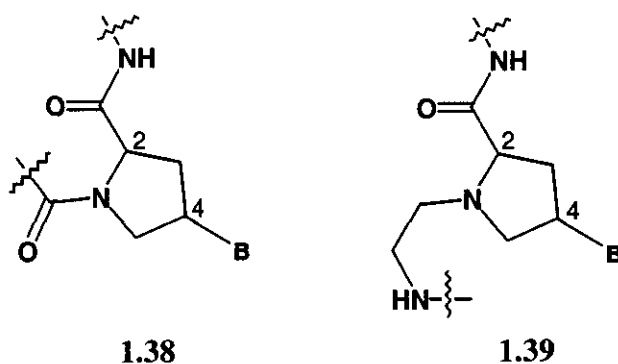
Comparison of this with the generalised PNA structure reveals the α -carbon of the glycine unit and the β -carbon of the adjacent ethylenediamine unit are bridged *via* a methylene group. The precursors required for such oligomers are the 4-(*R/S*)-amino- N^{α} -(A/G/C/T-ylacetyl)-2-(*R/S*)-prolines containing two asymmetric centers at C-2 and C-4 **1.37**.

Naturally occurring *trans*-4-hydroxyproline has been manipulated to access all four stereoisomers and has proved to be a useful starting material to synthesise such conformationally constrained PNA monomers. Oligomerisation of the four possible diastereoisomers has led to polychiral PNA having wide conformational diversity in the backbone.



1.37

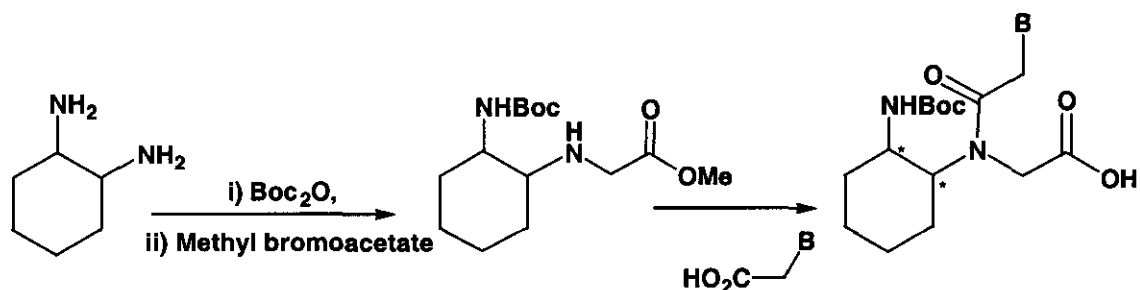
A similar strategy was later employed by Lowe²⁸ utilising 4-hydroxyproline to synthesise PNA monomers in which the nucleobase is positioned at C-4 of the pyrrolidine ring **1.38**.



This chiral PNA, based on a glycyl-*(S)*-proline skeleton, was shown to interact strongly with complementary DNA and RNA; however, it had poor solubility in aqueous media, making biological studies difficult. Lowe therefore synthesised a variant²⁹ that utilised a hydrophilic N-aminoethylproline backbone, **1.39**. This was readily soluble in aqueous medium and exhibited a strong interaction with oligoribonucleotides but not with oligodeoxyribonucleotides.

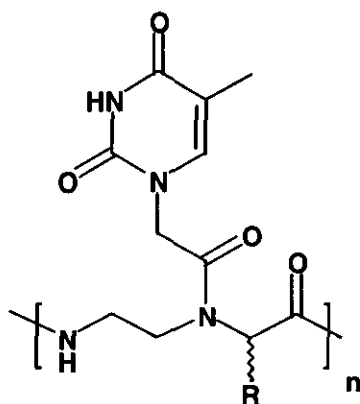
Another class of peptide nucleic acid monomer containing a cyclic system has been synthesised by Nielsen³⁰ (Scheme 1.2). The monomer has conformational restriction and the carbocyclic ring was also designed to increase the lipophilicity of the monomer. The monomers having a chiral backbone were prepared using the commercially available *cis* or *trans* isomers of 1,2-diaminocyclohexane. One amino group was protected as its Boc-derivative, the other was alkylated with methyl bromoacetate. The desired monomers

containing a chiral backbone were obtained by coupling to carboxymethyl functionalised purine or pyrimidine followed by basic ester hydrolysis.



Scheme 1.2

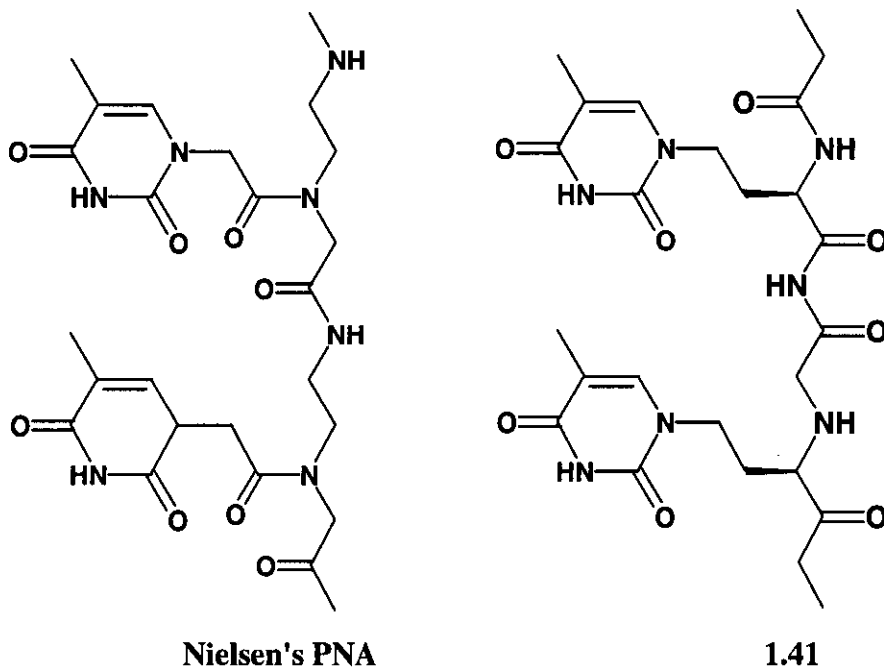
PNA containing amino acid having side chains



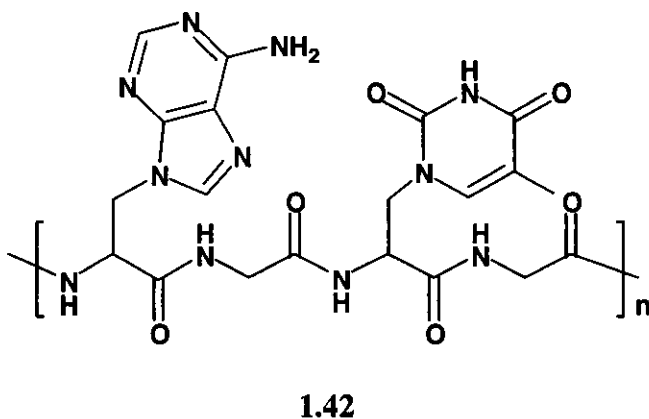
1.40

PNAs containing (*R*)-monomers (*R*-PNAs) **1.40** have been found to bind to the complementary antiparallel DNA with greater stability than do the corresponding (*S*)-PNAs³¹. The synthesis was effected using a similar strategy as in Scheme 1.2 but using lysine instead of glycine. The observed enantioselectivity has been explained in terms of preferential PNA helicity induced by the configuration of the stereogenic centre.

A final category of modification, in which we have been particularly interested, is that in which the nucleobase is incorporated as part of a side chain of an α -amino acid **1.41**.

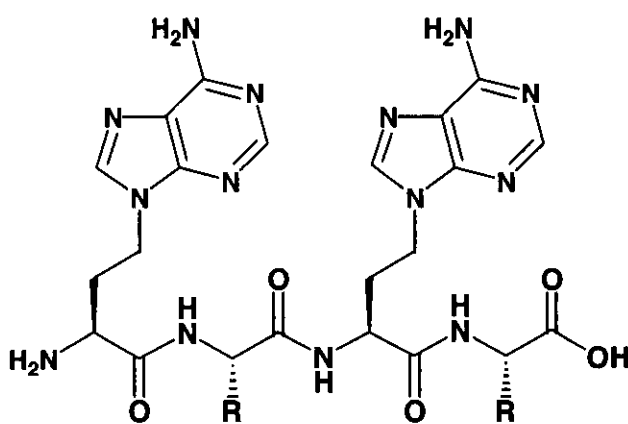


Taddei and co-workers have designed these building blocks in an attempt to enhance the rigidity of the PNA backbone, which is supposed to be one of the factors responsible for the binding of PNA to DNA. Taddei chose to prepare the self-complementary oligonucleotide ATATATAT **1.42**³².



The polypeptide backbone was composed entirely of α -amino acids and the distance between the nucleobases was the same as in the original PNA devised by Nielsen. Glycine was chosen as the spacer so that the structure would not be complicated by additional chirality. Lysine was chosen at the N-terminus to increase the solubility in aqueous media of this relatively low polarity structure. This PNA was indeed found to mimic DNA by forming a duplex with itself through Watson Crick base-pairing. However, the thermal stability of this complex was found to be lower than that of analogous PNA systems. However, the small number of bases employed in the structure and the fact that the semi-rigid peptide backbone may have some difficulty in adopting the double helical structure in solution may account for this low thermal stability. Nevertheless, it was demonstrated that a real chiral peptide nucleic acid with a structural backbone analogous to that of natural peptides could be prepared and that this product had some properties of typical nucleic acids.

Yamasaki³³ observed stable complex formation between dinucleotide analogues and complementary natural polynucleotides; again these dinucleotide analogues (eg. **1.43**) contain a true peptide backbone.



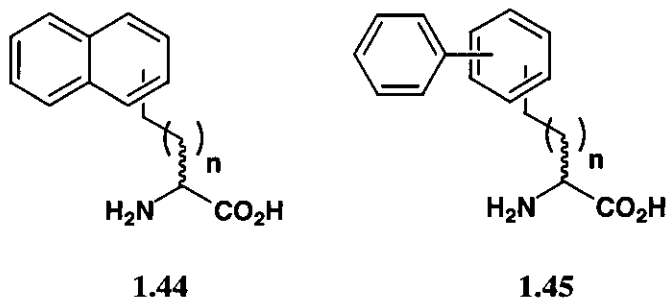
1.43

Indeed, he found that even these small dinucleotide-containing molecules showed good ability to form triplex structures. Moreover, analogues containing variation of the (alkyl)

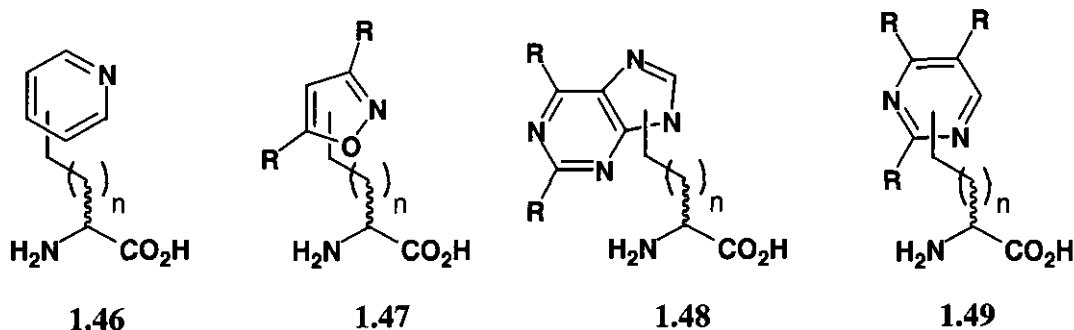
substituent at the α -position of the spacer amino acid unit showed very similar potency. A modification at this position with heterocycle-containing amino acids may be feasible to increase further the stability of the complexes or to modulate the DNA recognition ability.

1.3 Targets

The aim of the present work was to synthesise heterocyclic α -amino acids by selecting a stereoselective method of assembling amino acids and to apply it to targets such as those described in the previous section. More specifically our targets included cyclic and heterocyclic α -amino acids. Examples of this type included simple aryl groups such as naphthyl, **1.44**, and biphenyl, **1.45**, which could potentially serve as intercalating agents, and which were also used to test the synthetic method because the precursors do not necessitate any protecting group.

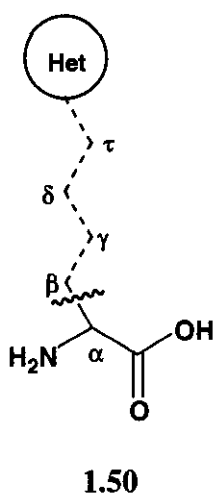


After establishing confidence in the method, we envisaged extending it to heterocycles containing one (pyridyl, **1.46**) or two (isoxazole, **1.47**) heteroatoms in the ring system (potential excitatory amino acid mimics) and then moving to the more challenging target, which constitute the main core of this thesis. In particular, our attention was focused on amino acids carrying heterocycles such as purine, **1.48** and pyrimidine, **1.49**, that contain two or more heteroatoms, for potential PNA application. These more valuable targets require manipulation of protecting groups so as to allow access to the desired molecules.



1.4 Strategies for assembling amino acids

To meet the demand for enantiomerically pure α -amino acids with specific non-proteinogenic functional groups, a large number of synthetic methods has been developed. For convenience, we have divided these into two main categories. The most synthetically challenging of these involves the asymmetric attachment, **1.50**, of either a nucleophilic or an electrophilic group to the α -carbon of a glycine equivalent. The second strategy involves attachment of the heterocycles at a bond beyond C_β (see **1.50**) to a chiral substituted glycine derivative.



The large number of synthetic methods available for the synthesis of enantiomerically pure amino acids is a reflection of the biological and chemical significance of such compounds. This section will focus on retrosynthetic strategies, highlighting those that have been employed in the most recent examples.

1.4.1 Attachment of heterocycles to a glycine equivalent

Retrosynthetic analysis involves seven different disconnections of the carbon-carbon bond at the asymmetric centre (Figure 1.2). Indeed the reaction of an electrophile or nucleophile in a stereoselective manner has been demonstrated to be most effective for the synthesis of heterocyclic amino acids. This is a very popular approach as it offers significant flexibility in the type of α -amino acid that can be produced. One of the main disadvantages of this method is that very often a chiral auxiliary is required to induce or create the stereochemistry at the α -centre. The harsh conditions often required to cleave the chiral auxiliary, and a requirement for purification to remove traces of chiral auxiliary, can limit the use of such approaches.

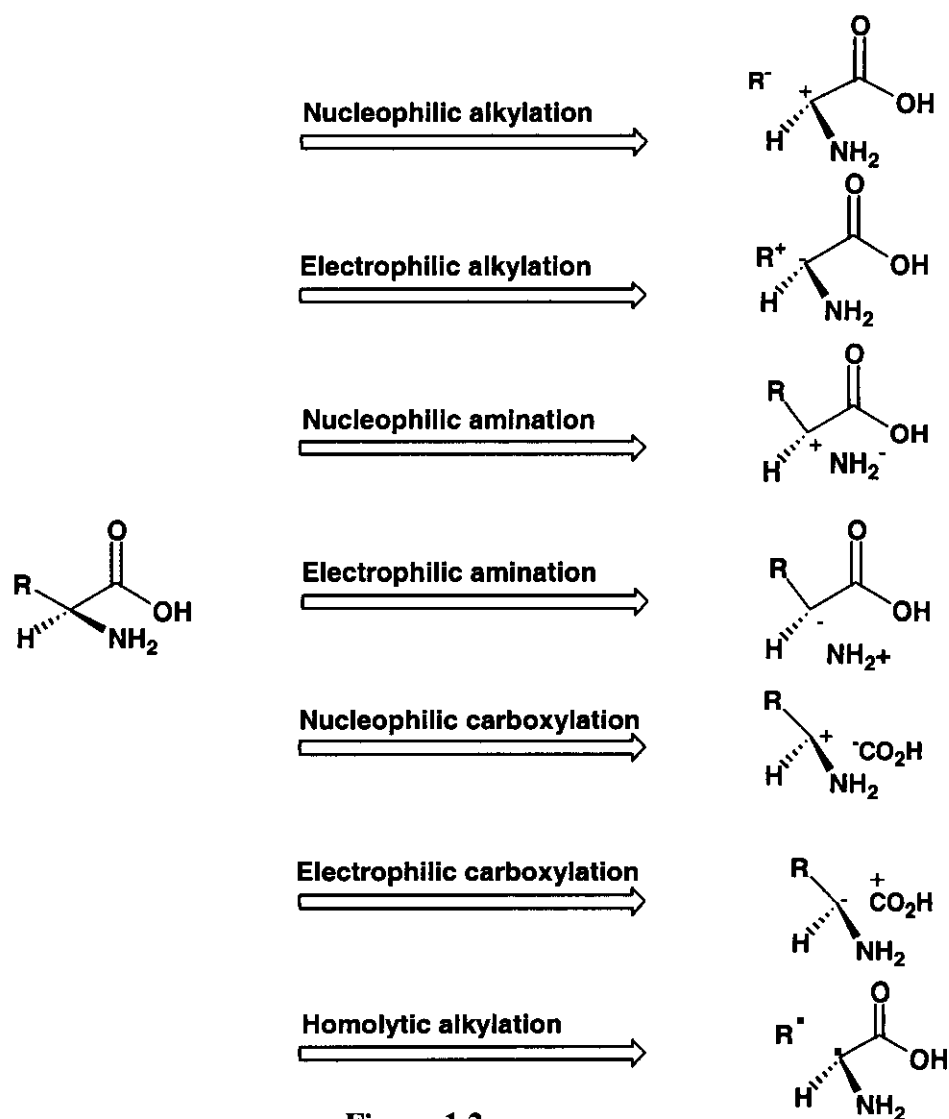
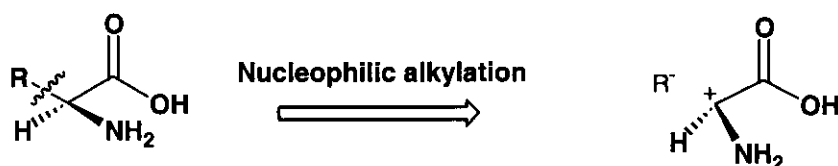


Figure 1.2

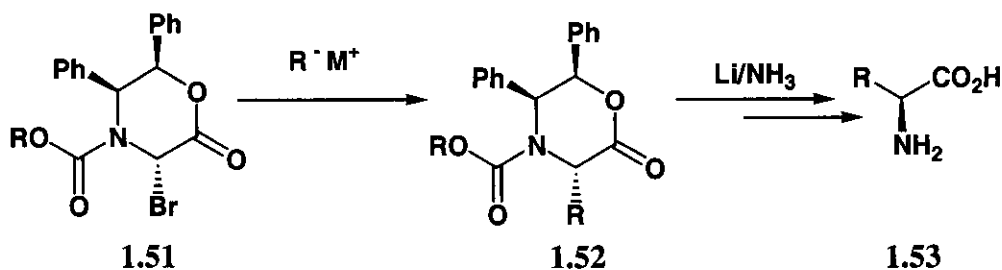
Each disconnection will now be discussed in turn and illustrated.

1.4.1.1 Nucleophilic alkylation



Scheme 1.3

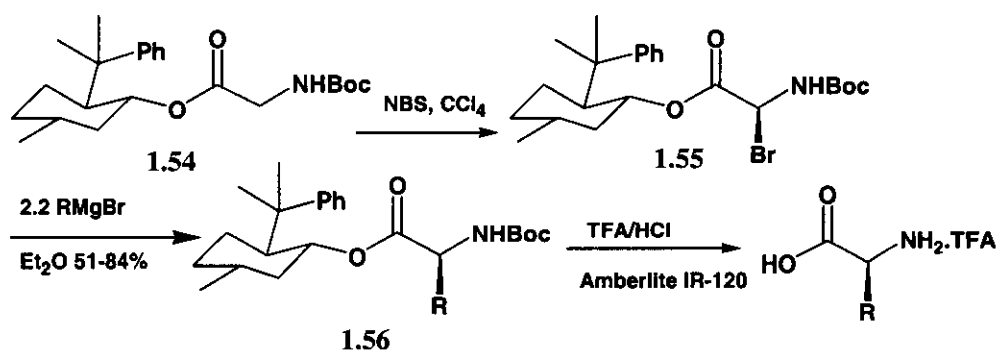
This method has received limited attention as the number of functional groups compatible with an organometallic nucleophile is restricted. One of the most thoroughly studied glycine cation equivalents is the 3-bromooxazinone **1.51**^{34, 35}.



Scheme 1.4

This has been successfully substituted with retention of configuration by malonate, alkyl zinc halides and cuprates (Scheme 1.4).

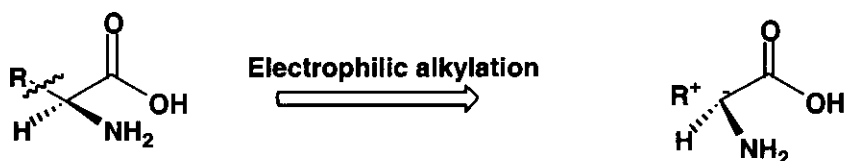
Using chiral esters as electrophilic glycine templates can also provide α-amino acids in high enantiomeric excess. When 8-phenylmenthyl ester **1.54** was used as the auxiliary, the α-bromoglycinate **1.55** was prepared as a single stereoisomer by reaction with N-bromosuccinimide³⁶ (Scheme 1.5).



Scheme 1.5

This intermediate was then reacted with a Grignard reagent to form first an imine that was stereoselectively attacked by a second equivalent of Grignard reagent to give **1.56**. Subsequent acid cleavage of the ester afforded the α -amino acids.

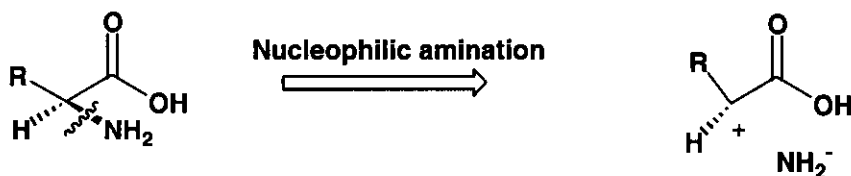
1.4.1.2 Electrophilic alkylation



Scheme 1.6

This strategy will be discussed in more detail in the next chapter, as one of the methods utilised in this thesis involves electrophilic alkylation of a glycine enolate equivalent.

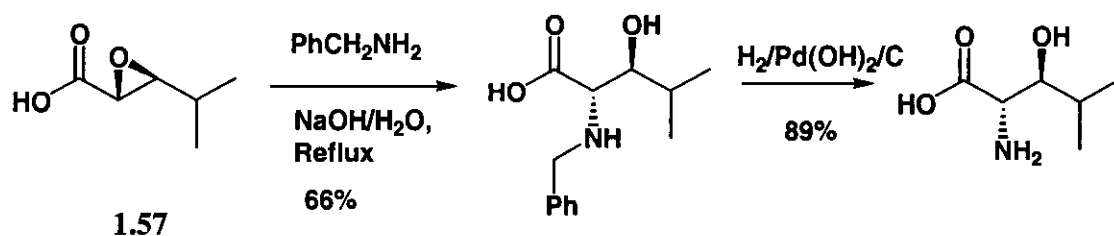
1.4.1.3 Nucleophilic amination



Scheme 1.7

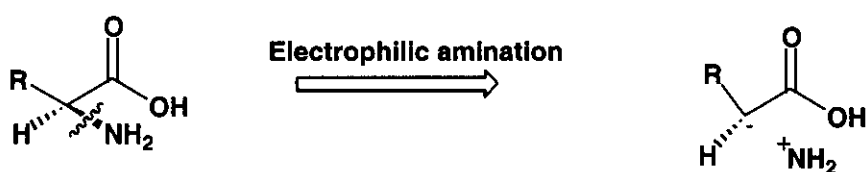
The generation of α -amino acids by introduction of the NH_2 group through the use of nucleophilic aminating agents is generally based on $\text{S}_{\text{N}}2$ displacement, the chirality being developed prior to nucleophilic amination. Versatile intermediates for this procedure are chiral epoxides (e.g. **1.57**). Benzylamine, for example, can act as an efficient nucleophilic

aminating agent for the formation of optically pure α -amino acids *via* intermolecular reaction with a suitable epoxide³⁷ (Scheme 1.8).



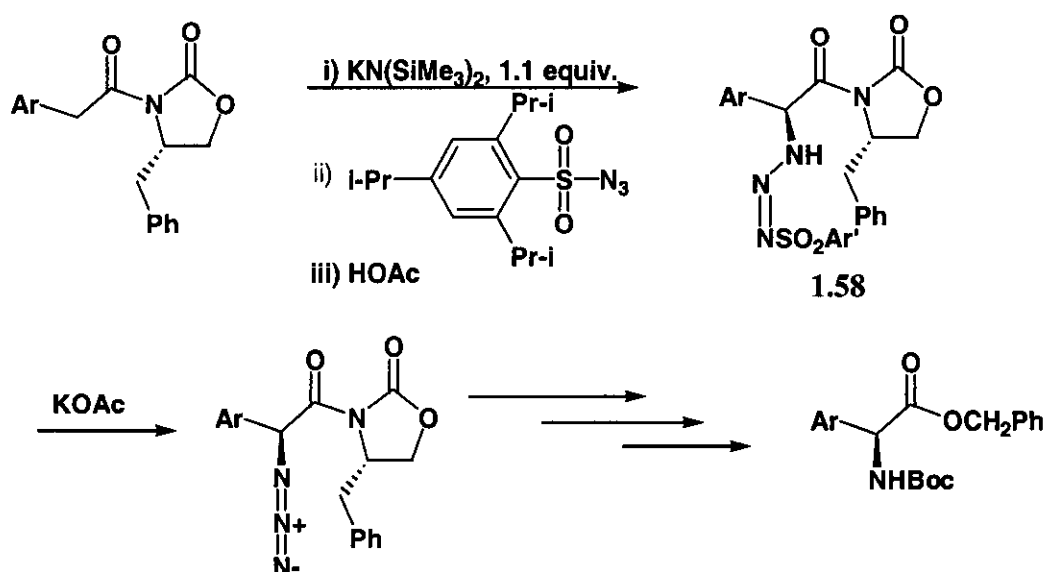
Scheme 1.8

1.4.1.4 Electrophilic amination



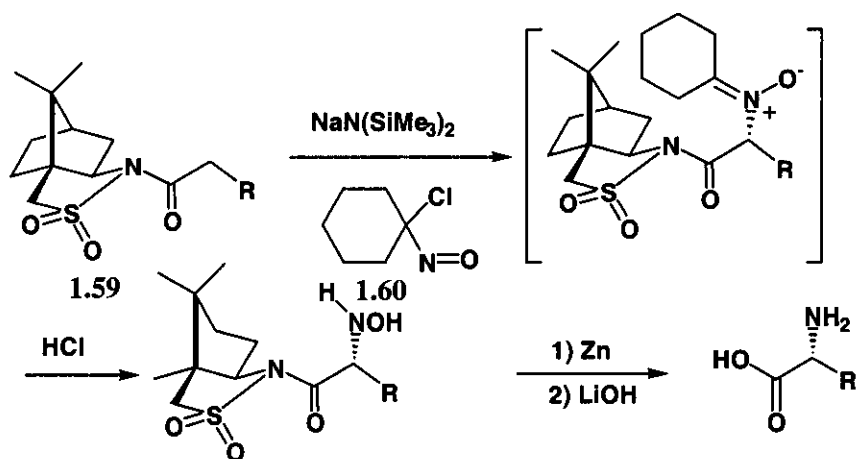
Scheme 1.9

Another direct approach to α -amino acids is the amination of enolates with electrophilic reagents. A promising electrophilic amination reagent, which has been introduced by Evans *et al.*³⁸ and has been used mainly for the preparation of complex amino acids (Scheme 1.10), is triisopropylbenzenesulfonyl azide.



Scheme 1.10

Oppolzer *et al.* have disclosed another procedure for enantioselective electrophilic amination of enolates based on the N-acylcamphorsultam **1.59** as chiral template and using 1-chloro-1-nitrosocyclohexane **1.60** as the nitrogen electrophile (Scheme 1.11)³⁹.



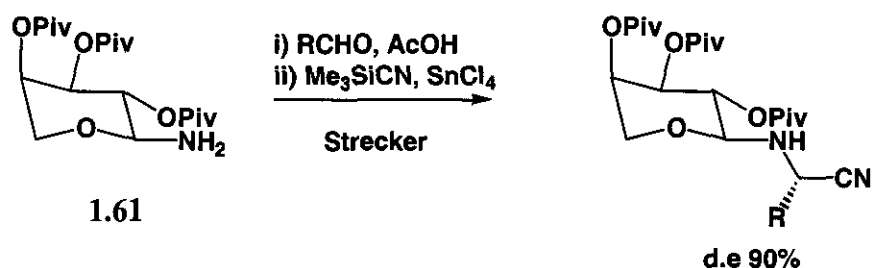
Scheme 1.11

1.4.1.5 Nucleophilic carboxylation



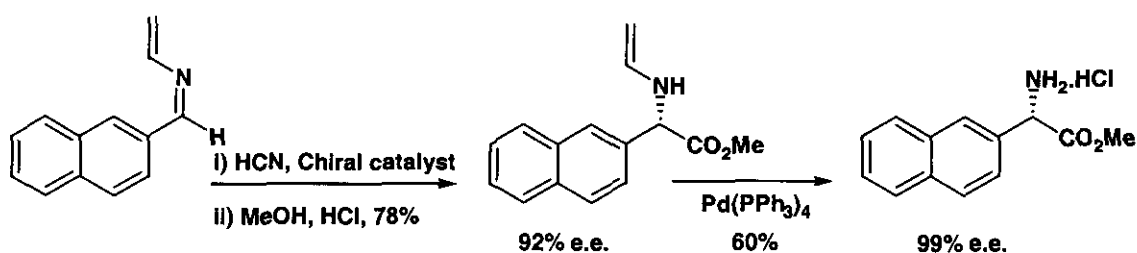
Scheme 1.12

This approach is usually associated with the Strecker reaction (Scheme 1.13) that typically utilises stereochemically pure carbohydrate-derived amines (**1.61**)⁴⁰. The nucleophilic carboxylate synthon in the Strecker synthesis is the cyanide ion. Stereocontrol can be expected by incorporating chirality in the aldehyde, the amine, and the nucleophile or by using a chiral catalyst.



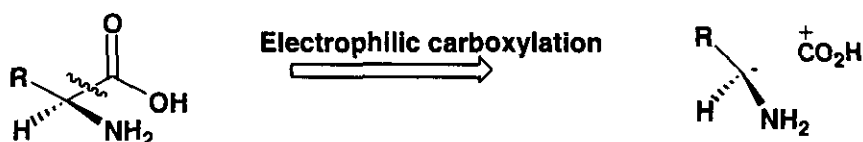
Scheme 1.13

The key step in the Strecker reaction relies on the nucleophilic addition of cyanide ion to the C=N bond of an imine, the nitrile functionality being then converted into the carboxylic acid, generally by acid hydrolysis. Some asymmetric versions of this reaction have been described giving α -amino acids with an enantiomeric excess of up to 99% (Scheme 1.14)⁴¹.



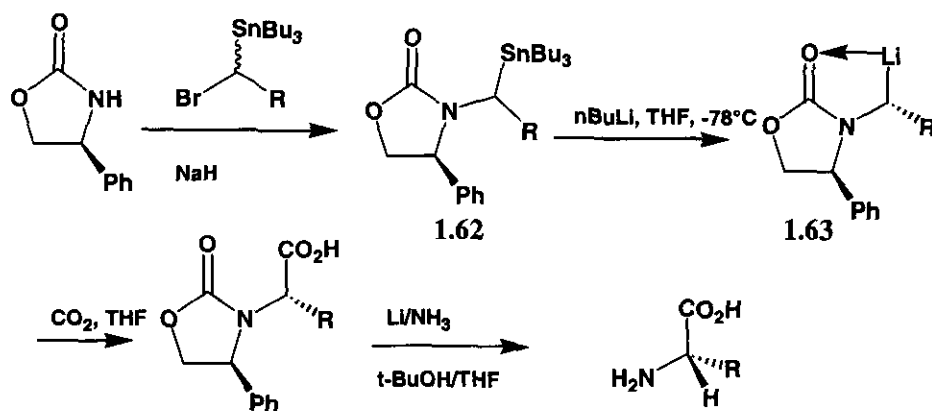
Scheme 1.14

1.4.1.6 Electrophilic carboxylation



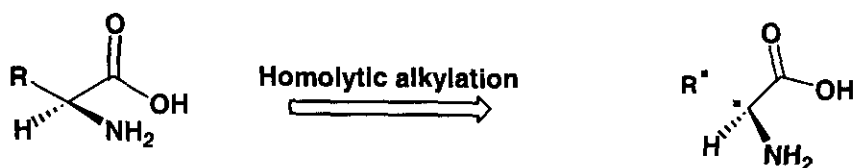
Scheme 1.15

Fournet *et al.*⁴² recently described the synthesis of enantiomerically pure α -amino acids by carboxylation (CO_2 gas) of N-(α -lithioalkyl)oxazolidinone (**1.63**) reagents obtained by the tin-lithium exchange of N-(α -stannylalkyl)oxazolidinones **1.62** (Scheme 1.16). This extended a method originally designed for methionine to other amino acids and was applied to the synthesis of *S*-leucine, *S*-alanine and *S*-homocysteine in *ca.* 80% yield and with enantiomeric excesses superior to 90%.



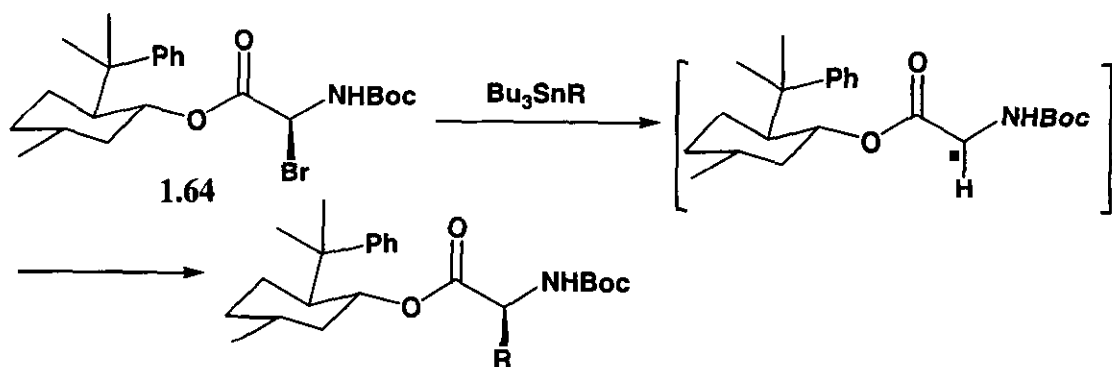
Scheme 1.16

1.4.1.7 Homolytic alkylation



Scheme 1.17

The asymmetric formation of α -amino acids by reaction of stannanes with a chiral α -bromo glycine ester (**1.64**) is one of the radical strategies that has been reported^{43,44} (Scheme 1.18).



Scheme 1.18

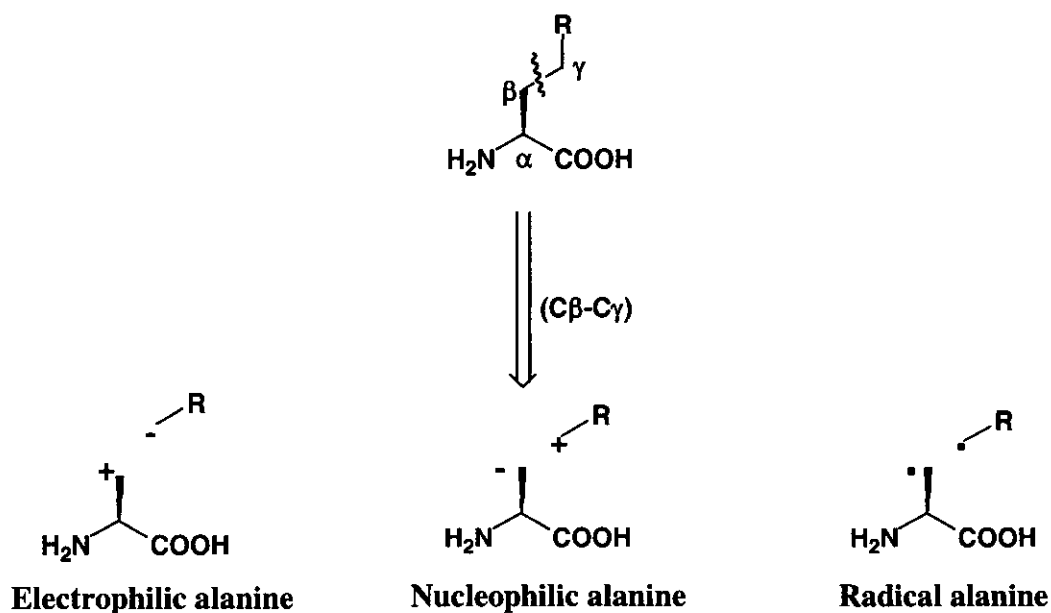
The general radical strategy will be discussed in more detail in Chapter 3 since we have used such an approach to make our heterocyclic amino acids.

This brief overview demonstrates the approaches that have been used to generate stereoselectively a chiral centre at the α -carbon atom. The remainder of this introduction

will detail an alternative strategy that involves the construction of α -amino acids by modification of the side chain of a readily available α -amino acid, retaining the level of stereochemical purity.

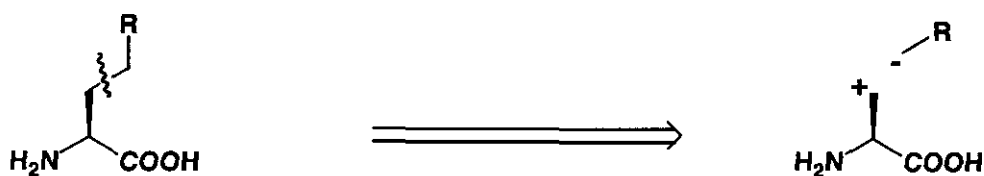
1.4.2 Attachment of heterocycles to substituted glycine

Work in this area has concentrated on the formation of the C_β - C_γ bond from electrophilic, nucleophilic and radical based synthons (Scheme 1.19) that are generated from alanine, serine, cysteine or aspartic acid and this will constitute the first sub-section of this survey. In a second sub-section, we will concentrate on the synthesis of α -amino acids by formation of bonds beyond C_γ .



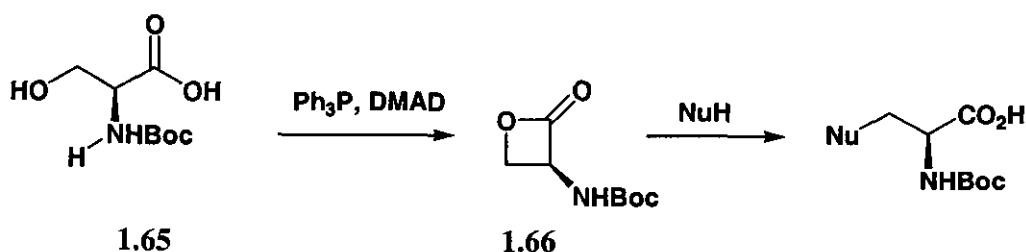
Scheme 1.19

1.4.2.1 Electrophilic alanine



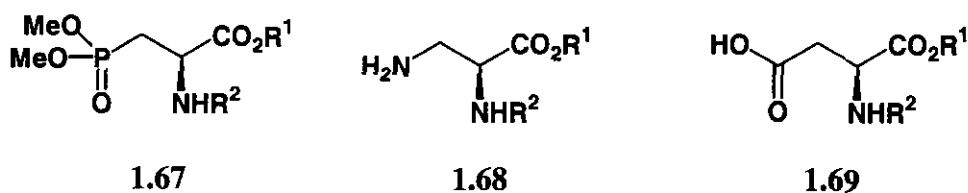
Scheme 1.20

The two most common β -cationic α -amino acid synthetic equivalents are derived from serine and cysteine. This concept is most readily realised by substitution of the serine OH-function after suitable activation. To avoid competing elimination, Vederas and coworkers have prepared the β -lactones **1.66** by Mitsunobu esterification from N-Boc-serine⁴⁵ **1.65** (Scheme 1.21).

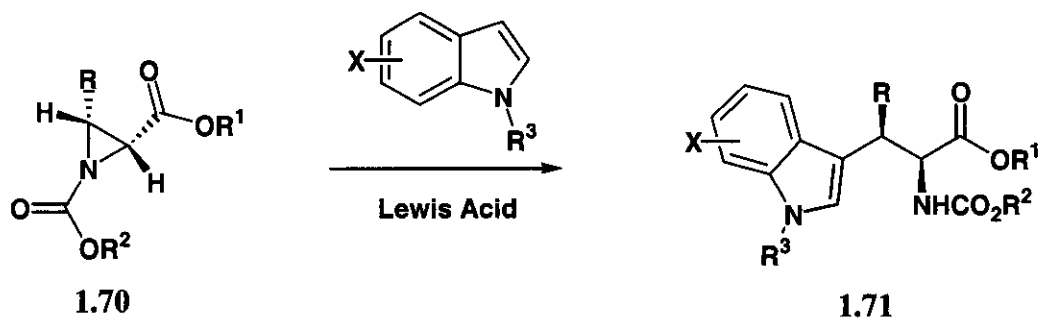


Scheme 1.21

Substituted alanines were obtained with various heteronucleophiles. Heating with phosphites resulted in an Arbuzov-like substitution to β -phosphoalanine **1.67**⁴⁶. The nucleophilic substitution can also be effected with ammonia, giving access to 2,3-diaminopropanoates **1.68**⁴⁷, but a competitive reaction occurs which is the formation of the serine amide resulting from the attack at the carbonyl group. By using cyanide ion as the nucleophile, the resulting β -cyano amino acid derivative could be hydrolysed to the aspartate **1.69**⁴⁸.

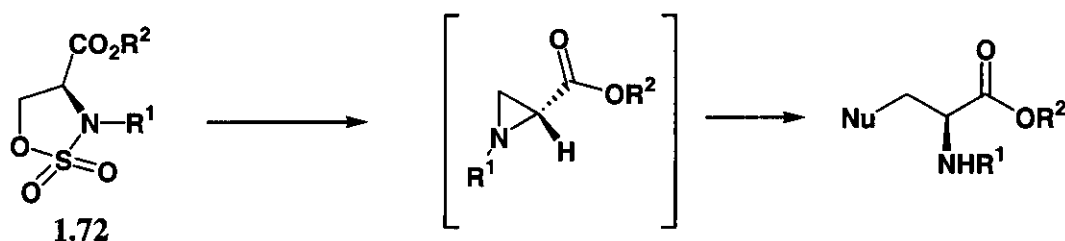


Heterocyclic amino acids can be obtained by a Lewis acid catalysed alkylation of the aziridine carboxylate **1.70** with various indoles to yield substituted tryptophans **1.71**⁴⁹ (Scheme 1.22).



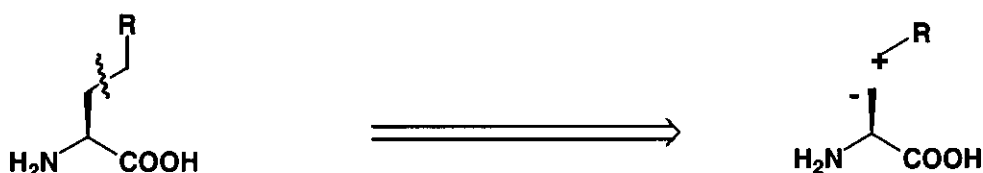
Scheme 1.22

Baldwin and co-workers have used the serine sulfamate **1.72** as a substitute for aziridine carboxylate in substitutions with a variety of nucleophiles, including cyanide, pyrazole, and malonate⁵⁰ (Scheme 1.23).



Scheme 1.23

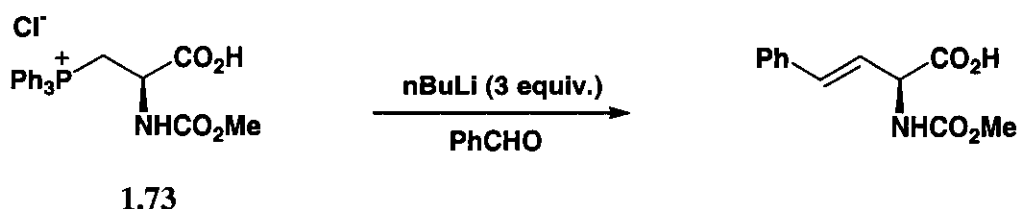
1.4.2.2 Nucleophilic alanine



Scheme 1.24

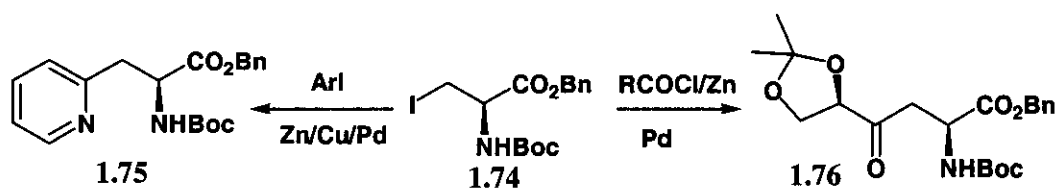
The polarity of the serine side-chain can be reversed from electrophilic to nucleophilic by utilisation of sulfone or phosphonium functionalities. For example, Itaya and co-workers⁵¹ have shown that the phosphonium chloride **1.73** can be prepared in 59% yield from

S-serine, and that the stereochemical integrity is retained completely upon reaction with *n*-BuLi and benzaldehyde (Scheme 1.25).



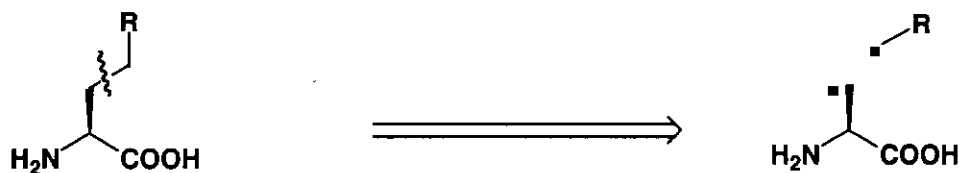
Scheme 1.25

Jackson *et al.* have reported the preparation of β -iodoalanine **1.74** and on the use of the corresponding Reformatsky reagent (Scheme 1.26). Aromatic iodides can also be used; for example, the pyridine analogue of phenylalanine, **1.75**, was obtained in moderate yield⁵². Various acid chlorides have also been coupled using catalytic palladium, an example being the glyceric acid derivative **1.76**⁵³.



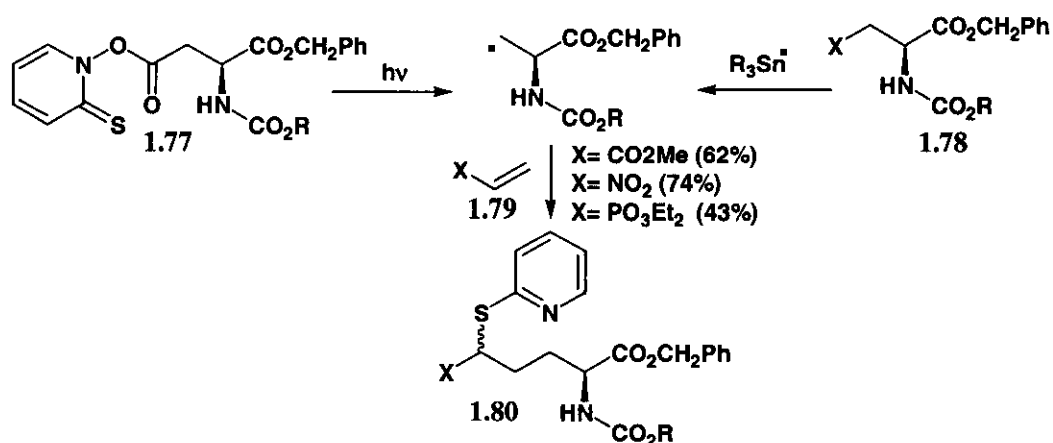
Scheme 1.26

1.4.2.3 Radical alanine synthetic equivalent



Scheme 1.27

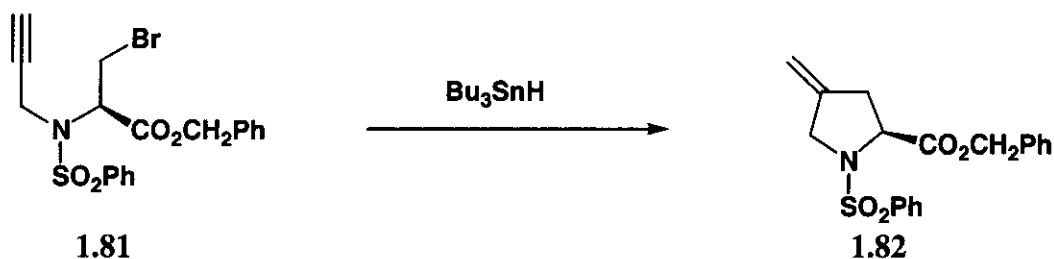
The C_β radical can be obtained by photolysis of the Barton ester of aspartic acid **1.77**^{54,55,56} or from homolytic cleavage of a β -haloalanine **1.78** with a tin radical.



Scheme 1.28

Radical traps include electrophilic olefins **1.79** that give adducts **1.80** in good yields.

The radical addition can also occur in an intramolecular fashion (Scheme 1.29). Treatment of an N-allyl or N-propargyl- β -haloalanine (**1.81**) derivative with tributyltin hydride leads to proline derivatives (**1.82**)⁵⁷.



Scheme 1.29

1.4.2.4 Bond formation beyond C_γ

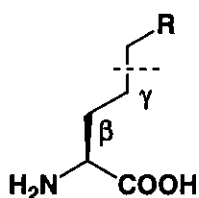
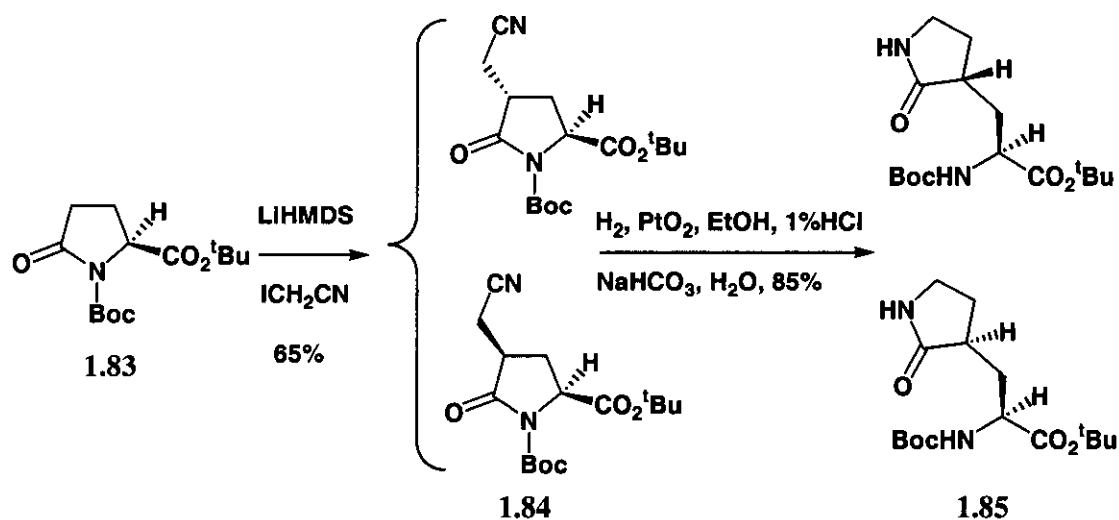


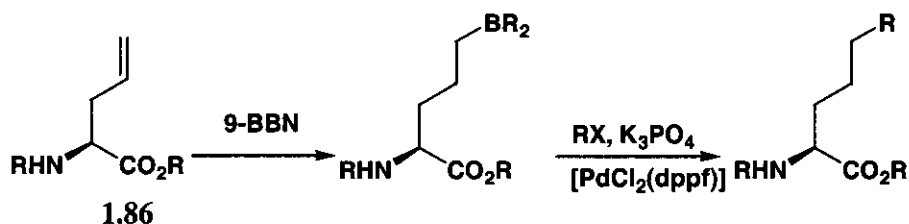
Figure 1.2

(*S*)-Pyroglutamic acid **1.83** can serve as a building block to effect transformations beyond C_γ and Murray has utilised the lactam **1.84** to prepare a range of pyrrolidones⁵⁸. Each diastereoisomer of **1.84** was further elaborated to give a range of heterocyclic amino acids.



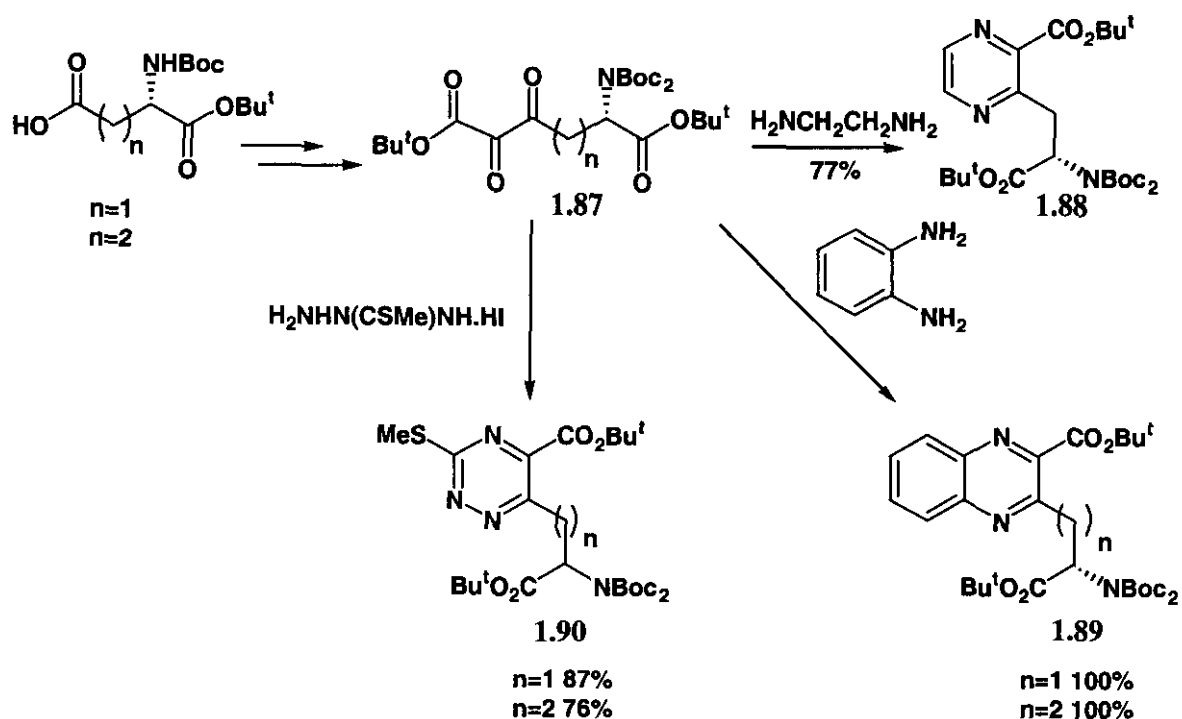
Scheme 1.30

Taylor has used a borane methodology based on allylglycine **1.86**, and has carried out a hydroboration-Suzuki cross-coupling sequence using a range of unsaturated halides⁵⁹.



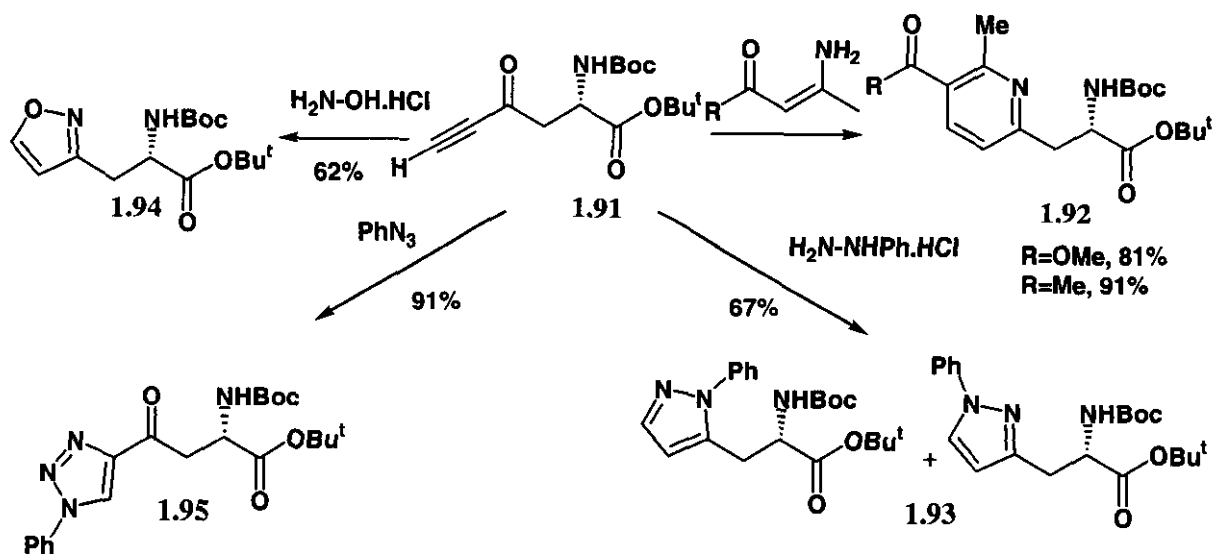
Scheme 1.31

Another starting template for the synthesis of heterocyclic α -amino acids by construction of bonds beyond C_γ is the vicinal tricarbonyl **1.87**, which is easily accessible from glutamic ($n=2$) or aspartic acids ($n=1$). Reaction of **1.87** with ethylenediamine (Scheme 1.32) gave the desired pyrazine substituted amino acid **1.88**⁶⁰. A cyclocondensation with 1,2-diaminobenzene resulted in conversion to the quinoxaline substituted α -amino acids **1.89**. The 1,2,4-triazine **1.90** was also achieved in good yield by reaction with *S*-methyl isothiosemicarbazide. No investigation of potential racemisation during the cyclocondensation was reported.



Scheme 1.32

Baldwin *et al.*⁶¹ have used a propargyl functionality **1.91**, created from aspartic acid,⁶² to synthesise a range of non-proteinogenic heterocyclic amino acids (Scheme 1.33).



Scheme 1.33

1.5 Summary

The aim of this project was the synthesis of unnatural heterocyclic α -amino acids. Indeed, first, they represent important targets as some are present as natural products. We have shown that the heterocycle itself is the key that can govern the activity in a peptide unit and in many cases the heterocycle is responsible for the binding to the substrate. Moreover, the synthesis of amino acids is important for the design of DNA mimics. More recently nucleic acid bases bearing amino acids have attracted a lot of attention in the design of novel peptide nucleic acids. The methods to synthesise heterocyclic amino acids are numerous and are governed by the structure of the heterocycle. In this work, we have chosen first to use an anionic route and secondly a radical method, this will constitute the two main chapters of this thesis.

CHAPTER 2

A GLYCINE ENOLATE APPROACH

2.1 Methods available

As outlined in the general introduction, one possibility for retrosynthetic disconnection at the α -carbon of amino acids corresponds to the introduction of the complete side chain R by electrophilic attack on a glycine enolate (Scheme 2.1),

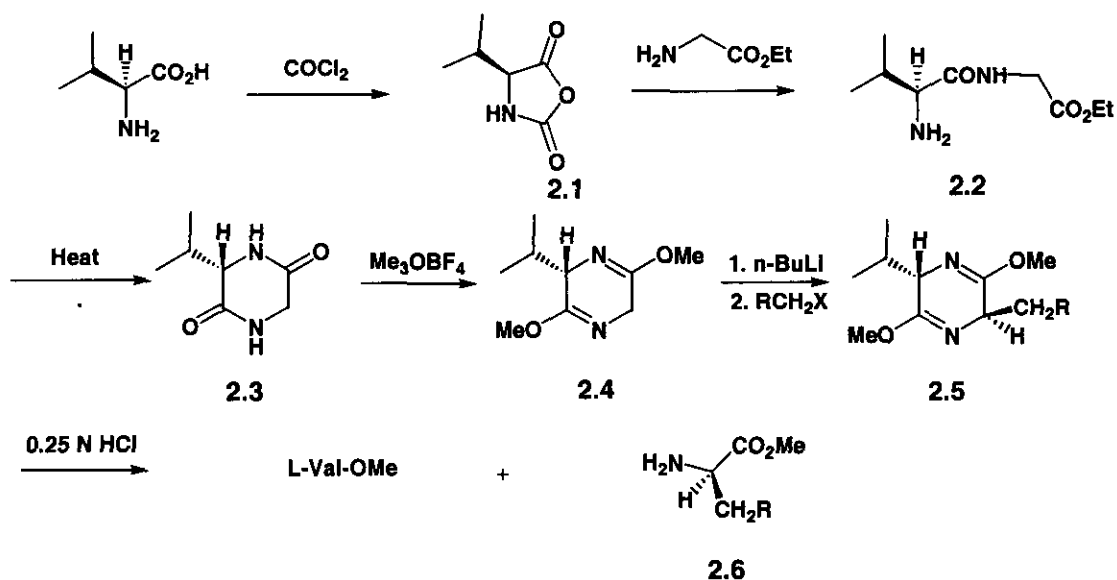


Scheme 2.1

This approach will now be elaborated further, with an overview of the most important methods available, and with highlights of their respective advantages and weaknesses.

2.1.1 Bis-lactim ethers

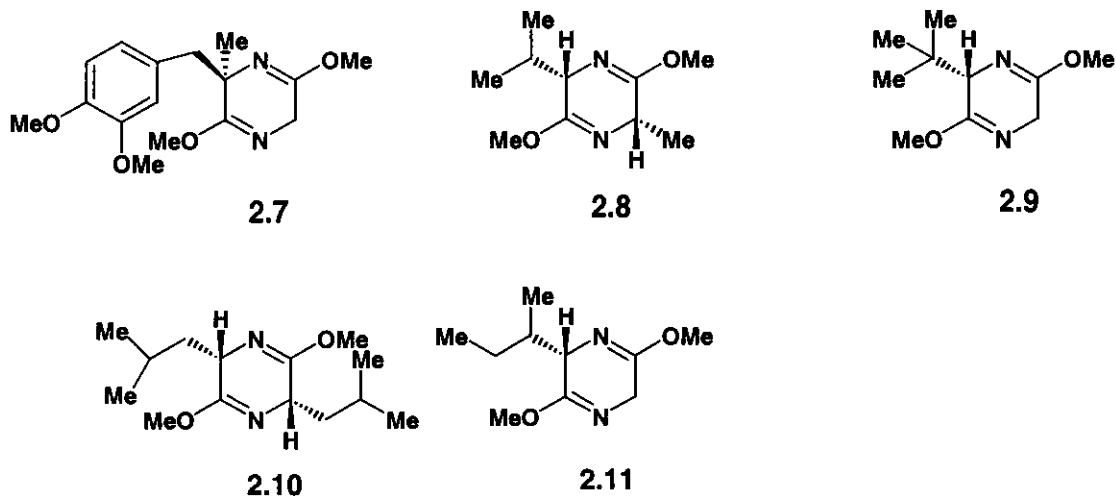
The introduction of the chiral bis-lactim ether, e.g **2.4**, as a glycine enolate equivalent was made by Schöllkopf and coworkers⁶³. This method, useful for the preparation of a large variety of amino acids, is based on the metallation and subsequent alkylation of the bis-lactim ether **2.4** (Scheme 2.2).



Scheme 2.2

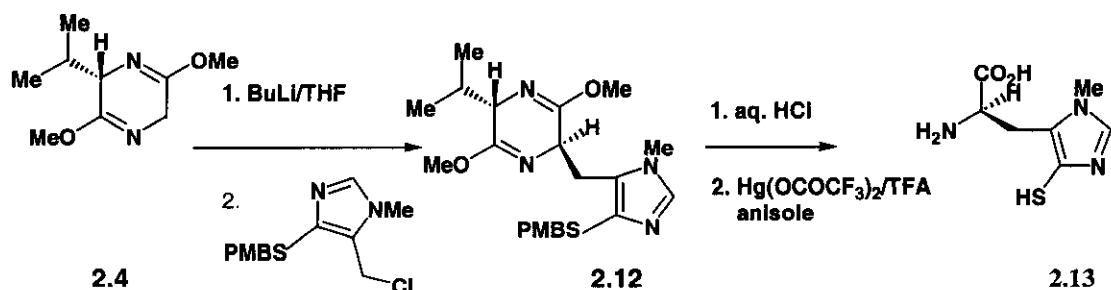
The general procedure involves formation of the chiral piperazinedione **2.3** and subsequent bis-lactim ether formation with trimethyloxonium tetrafluoroborate. The most popular and extensively studied bis-lactim ether is that derived from *S*-valine and glycine. Metallation of the bis-lactim ether with butyllithium in THF at low temperature and subsequent alkylation with a variety of electrophiles gives the anti-adducts **2.5** with a high degree of stereoselectivity. Hydrolysis of the heterocycle using dilute hydrochloric acid furnishes the new amino acid methyl ester **2.6** (usually the (*R*)-enantiomer) and (*S*)-valine methyl ester which must be separated.

Several other bis-lactim ethers have been prepared following this standard protocol including systems derived from (*S*)-O,O-dimethyl- α -methyldopa and glycine **2.7**, (*S*)-valine and alanine **2.8**, (*S*)-*tert*-leucine and glycine **2.9**, (*S*)-leucine and (*S*)-leucine **2.10**, (*S*)-isoleucine and glycine **2.11** (Scheme 2.3).



Scheme 2.3

Employing the Schöllkopf template **2.4**, Hopkins *et al.* prepared ovothiol A⁶⁴ **2.13**, found in the eggs of certain marine invertebrates, *via* alkylation using N-methyl-4-(*p*-methoxybenzylthio)-5-chloromethylimidazole, chromatographic separation of the 5:1 *anti:syn* mixture of diastereoisomers and hydrolysis of the bis-lactim ether **2.12** (Scheme 2.4).

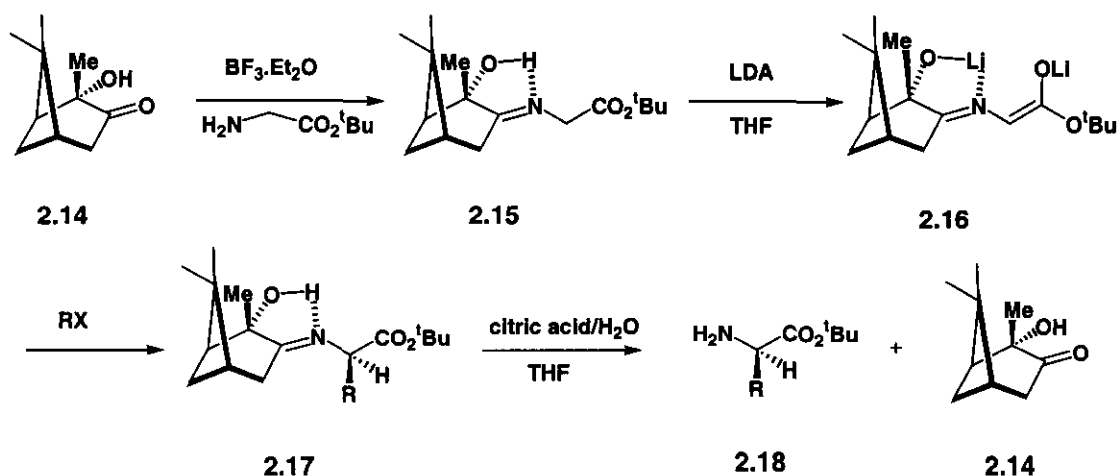


Scheme 2.4

Although, the bis-lactim ether method provides a powerful and versatile tool for preparing a large array of α -amino acids, a weakness of the method is the difficulty encountered in the hydrolysis of the derivatised bis-lactim ethers first to the amino acid methyl esters and subsequently, under harsher conditions, to the free amino acids.

2.1.2 Asymmetric enolate alkylation of Schiff bases

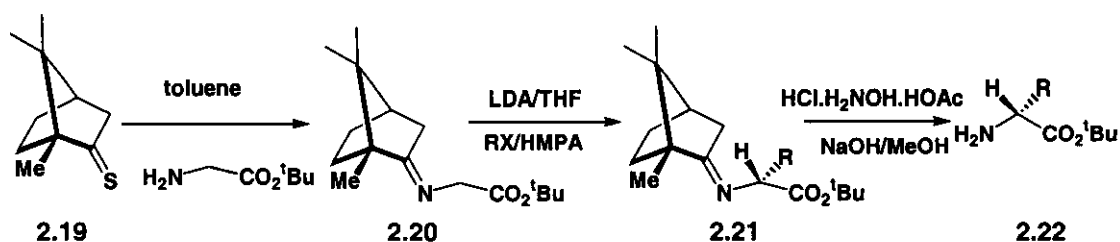
One of the first reports on the stereoselective alkylation of glycine imines was that by Yamada *et al.* in 1976⁶⁵. In this strategy, Scheme 2.6, condensation of (1*S*,2*S*,5*S*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one **2.14** with glycine *tert*-butyl ester in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave the ketimine **2.15**. Treatment with 2 equivalents of LDA in THF led to the chelated dilithio species **2.16**, and subsequent alkylation proceeded stereoselectively to give **2.17**. Hydrolysis of the ketimine with aqueous citric acid in THF provided the *tert*-butyl esters **2.18** that could be cleaved to the free amino acids.



Scheme 2.6

McIntosh and coworkers⁶⁶ have used a similar strategy based on camphor-derived imines of glycine (Scheme 2.7). Camphor itself was found to be too sterically hindered to condense directly with glycine esters to form the Schiff base; instead the more reactive thione **2.19** was used. Conversion of the intermediate imines **2.21** to the *tert*-butyl esters **2.22** required hydroxylamine, as steric hindrance makes hydrolysis of the camphor imine difficult. However, the inconsistent stereoselectivity, which is dependent on the structure

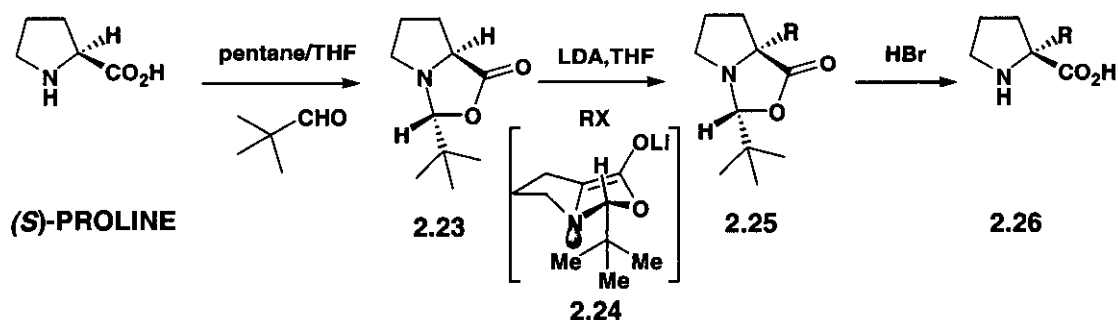
of the electrophile, and the tricky final cleavage of the hindered imine are factors which have limited the application of this method.



Scheme 2.7

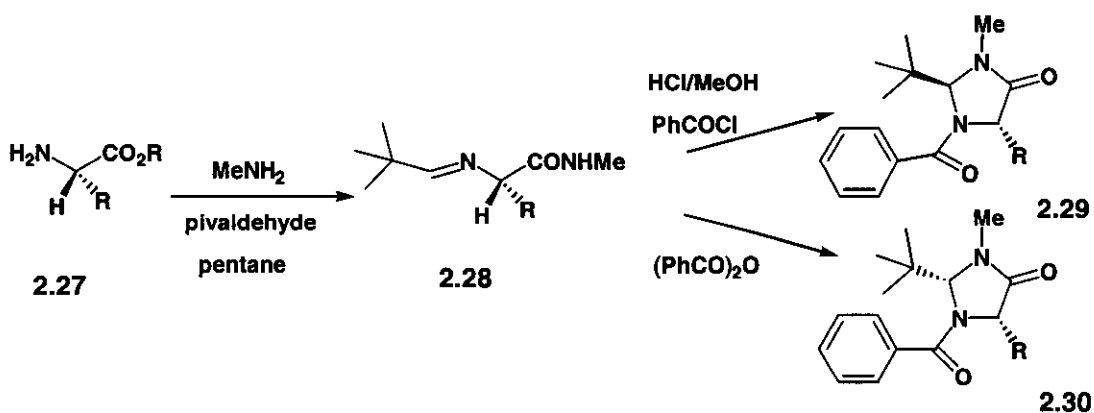
2.1.3 Oxazolidinones and imidazolidinones

The use of the oxazolidinone system is exemplified by compound **2.23** which can be prepared from (*S*)-proline and pivaldehyde⁶⁷ (Scheme 2.8). Here, the stereogenic centre of proline controls the stereoselectivity in the formation of the C-2 stereogenic centre of the oxazolidinone. Treatment of **2.23** with LDA in THF afforded the planar enolate **2.24** that has lost the chirality associated with the proline ring. However, the enolate underwent highly diastereoselective alkylation controlled by the *tert*-butyl group with retention of configuration.



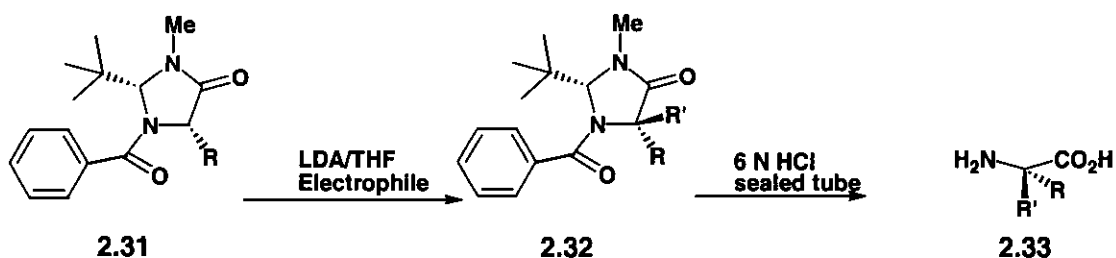
Scheme 2.8

The imidazolidinone approach is illustrated in Scheme 2.9⁶⁸. Pivalyl imines **2.28** of amino acid *N*-methyamides readily form the *anti*-imidazolidinone **2.29** upon treatment with methanolic HCl followed by acylation with benzoyl chloride. The corresponding *syn*-isomers **2.30** are available by treatment of **2.28** with benzoic anhydride.



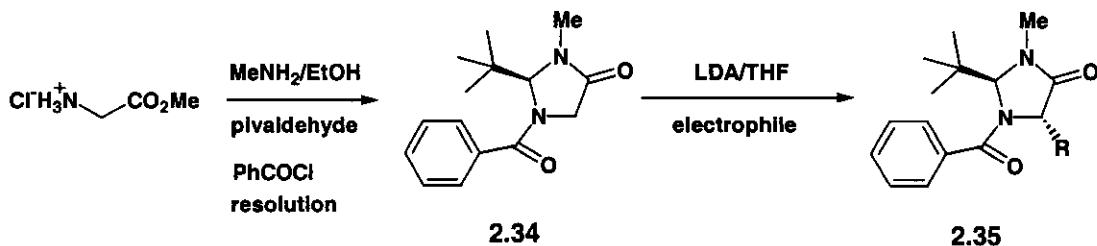
Scheme 2.9

Valine, phenylglycine, phenylalanine, aspartic acid and glutamic acid have all been converted into the corresponding imidazolidinones. Alkylation of the enolates derived from these to afford **2.32** proceeded in good yield and with excellent diastereoselectivity, (Scheme 2.10). However, a real disadvantage of these systems is the final hydrolysis which requires severe conditions, typically 6 M hydrochloric acid in a sealed tube.



Scheme 2.10

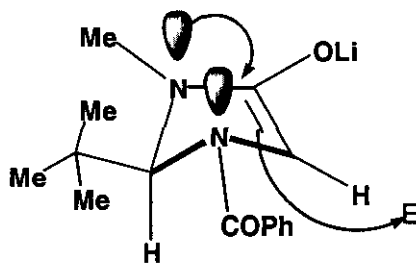
Significantly, the corresponding glycine derivatives have also been examined⁶⁹. Alkylation of the enolate derived from **2.34** proceeded with high stereoselectivity to afford **2.35**.



Scheme 2.11

It is thought that the enolate adopts a conformation that places the *tert*-butyl group in a pseudo-equatorial position, and that both nitrogen atoms are pyramidal with the lone pairs

pseudoaxial (Scheme 2.12). The combined steric effect of the *tert*-butyl group and the *anti*-stereoelectronic effect of the enamine favours the electrophilic attack *anti* to the *tert*-butyl group.

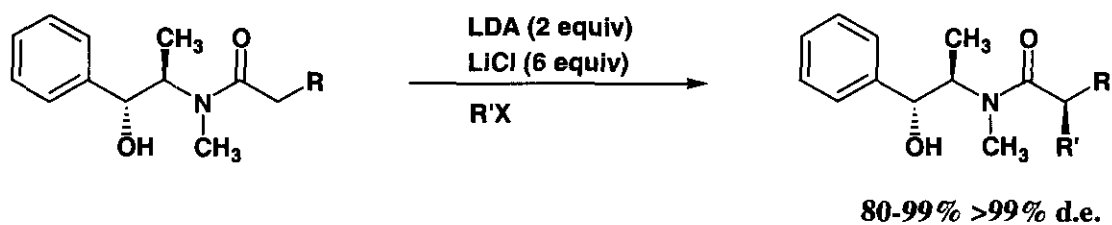


Scheme 2.12

The stereoselective functionalisation of these heterocycles *via* enolate methodology, has provided a useful and practical approach to the asymmetric synthesis of non-proteinogenic amino acids, again despite the somewhat harsh acidic conditions (6 M HCl) needed to provide the final amino acids.

2.1.4 Pseudoephedrine amides

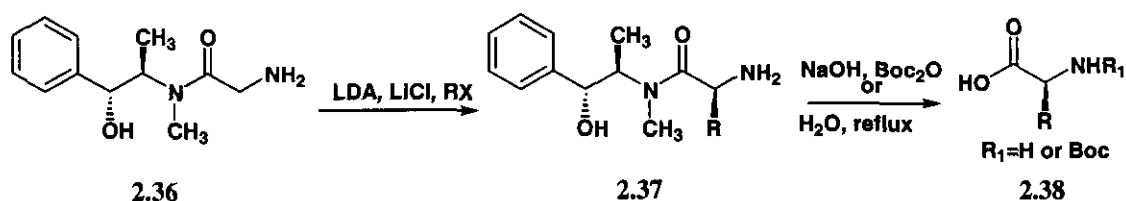
In recent publications, Myers and co-workers⁷⁰ have described a method for the alkylation of amide enolates using pseudoephedrine as a chiral auxiliary (Scheme 2.13). Pseudoephedrine was *N*-acylated in high yield (90-95%) using carboxylic acid chlorides and anhydrides. After deprotonation with LDA (2 equiv.), these *N*-acylpseudoephedrine derivatives reacted efficiently with alkyl bromides or iodides in a highly stereoselective manner. Furthermore, a number of simple cleavage reactions, with recovery of the chiral auxiliary, demonstrated the synthetic potential of these pseudoephedrine amides.



Scheme 2.13

Given that this process employs a stoichiometric amount of chiral auxiliary, it might appear to be non-competitive with asymmetric catalytic procedures (see Chapter 1). However, it is also important to consider (i) the low cost and (ii) the ready availability of both enantiomeric forms of pseudoephedrine, as well as (iii) the tendency of many pseudoephedrine amides to be crystalline, thus making the compounds easy to handle and purify. Overall, the alkylation reactions are highly diastereoselective, and given that each of the synthetic manipulations may be executed without the use of protecting groups this approach is highly attractive.

Myers has demonstrated (Scheme 2.14) that the pseudoephedrine-based methodology can be adapted for the synthesis of amino acids using pseudoephedrine glycineamide **2.36**^{71,72}. Such compounds can be alkylated at the α -carbon of the glycine moiety using similar conditions to those used for simple acyl groups. Diastereoselectivities of 95% have been reported. Formation of the desired amino acids **2.38** can be achieved with very high enantiomeric excess by cleavage of the amide bond under basic, acidic or neutral conditions.



Scheme 2.14

2.1.5 Summary

As shown above, the alkylation of an α -carbon of an enolate derivative of glycine is one of the most direct, general and commonly used methods for the preparation of α -amino acids. We selected for our purposes (namely the synthesis of new heterocyclic amino acids) the method developed by Myers because of its potential advantages over other enolate procedures. These include the low cost and availability of both enantiomers of pseudoephedrine, the tendency of pseudoephedrine amides to be crystalline, the high diastereoselectivities of the alkylation reactions, and the facile removal of the chiral auxiliary (which can be recycled). Lastly, each synthetic manipulation could be done without the use of a protecting group on the amino of glycine. Using this route, unnatural, salt-free, amino acids can be prepared in three steps in good yields and in high enantiomeric excess.

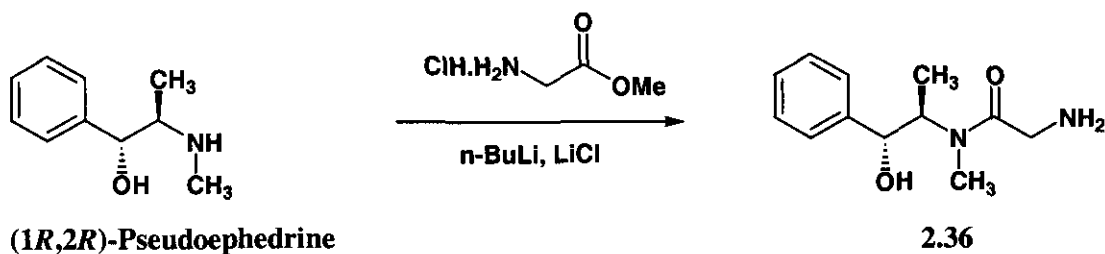
2.2 Results and discussion

This discussion will focus on the results obtained using pseudoephedrine as a chiral auxiliary and a range of heterocyclic electrophiles to access unusual amino acids containing heterocycles in their side chain. We will present first our validation of the method and subsequently describe its application to the synthesis of unusual heterocyclic amino acids. The determination of the enantiomeric purity of these unusual amino acids will also be presented.

2.2.1 Validation of the method

2.2.1.1 Pseudoephedrine glycineamide synthesis

The synthesis of pseudoephedrine glycineamide **2.36** was effected by direct condensation between (1*R*,2*R*)-pseudoephedrine and glycine methyl ester under basic conditions using a procedure developed by Myers⁷⁰ (Scheme 2.15).



Scheme 2.15

An initial attempt to neutralise the hydrochloride salt of glycine methyl ester hydrochloride using triethylamine (1 equiv.) in dry diethyl ether resulted in the formation of unwanted side-products in the later alkylation reaction. However, we found that treatment of glycine methyl ester hydrochloride in dry diethyl ether with dry ammonia for 3-4 h, followed by filtration of the ammonium chloride and careful concentration of the ethereal solution afforded a sufficiently pure solution of the free glycine methyl ester. In our hands, this method gave good yields in the subsequent coupling reaction (typically 70-80%). This coupling reaction is noteworthy in that the secondary amino group of pseudoephedrine was acylated by the carboxylic ester without any detectable competition from the amino group of glycine, thus obviating the need for protection of this functionality. The coupling protocol involved deprotonation of the hydroxyl group of pseudoephedrine (1 equiv.) with *n*-butyllithium (2.5M, 0.80 equiv.) in the presence of anhydrous lithium chloride (2 equiv.) in THF at 0°C and subsequent addition of the ethereal solution of glycine methyl ester (1.2 eq) in THF. It was noted that a high yield, typically 75%, was only obtained when rigorously anhydrous lithium chloride was used

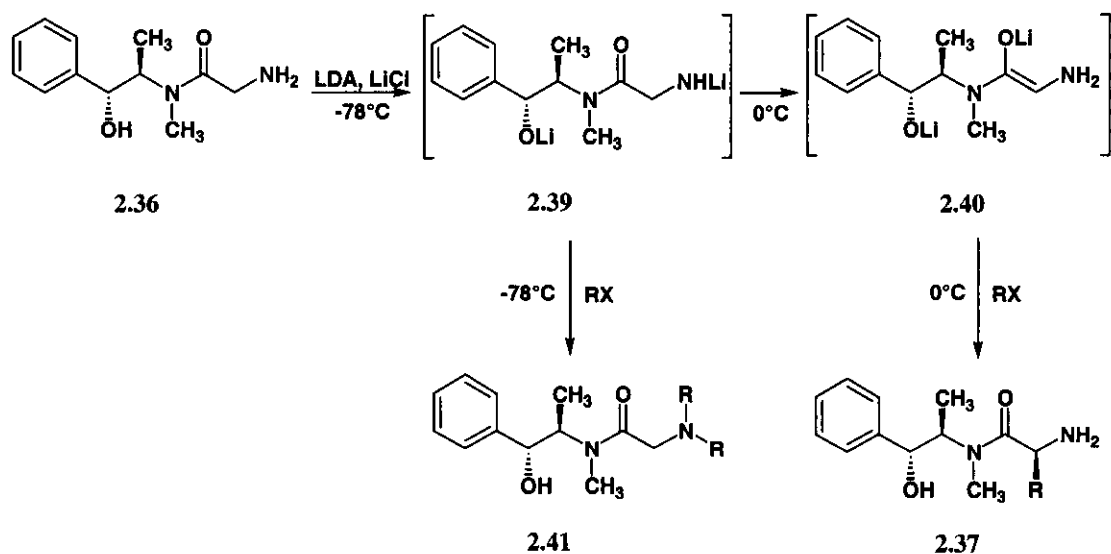
and also when very slow addition of glycine methyl ester (typically over 1.5 h) was carried out. Lithium chloride is believed to have an accelerating effect on the rate of the reaction thereby preventing self-condensation of glycine methyl ester. This accelerating effect is thought to result from activation of glycine methyl ester by bidentate coordination to the lithium cation. This coordination is also considered to diminish the nucleophilicity of the glycine amino group consequently decreasing the formation of by-products.

It is believed that this one step procedure of pseudoephedrine glycinamide formation proceeds by the initial transesterification of glycine methyl ester with the secondary hydroxyl group of pseudoephedrine, followed by a rapid O- to N-acyl transfer. Pseudoephedrine glycinamide was obtained first as the hydrate without any chromatography. Dehydration of pseudoephedrine glycinamide using anhydrous potassium carbonate and subsequent recrystallisation from toluene afforded anhydrous pseudoephedrine glycinamide. It is worth noting that failure to properly dehydrate pseudoephedrine glycinamide could lead to consumption of the strong base (LDA) needed in the alkylation process to enolize pseudoephedrine glycinamide. In the anhydrous state, pseudoephedrine glycinamide is a stable white solid which was typically stored in *vacuo* in the presence of phosphorus pentoxide to absorb any moisture.

2.2.1.2 Enolization of pseudoephedrine glycinamide

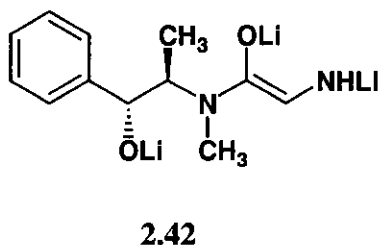
A unique feature of the use of pseudoephedrine glycinamide **2.36** as a chiral glycine enolate is the fact that the primary amino group is not protected. This introduces a potential complication in the enolization procedure as three different acidic functional groups are present in the molecule, namely the secondary hydroxyl group, the glycine α -carbon and the primary amino group. It has been confirmed experimentally by others that **2.39** is the

kinetic product of the reaction with 2 equiv. of base (Scheme 2.16). However, if the reaction mixture is allowed to warm up to 0°C prior to the addition of alkylating agent then equilibration to a thermodynamically more stable enolate **2.40** occurs and the C-alkylated product **2.37** is observed instead of the N-alkylated product **2.41** (which is observed at -78°C).



Scheme 2.16

Decomposition occurs when excess base (> 2 equiv.) is used. For example, with 2.2 equiv. of LDA pseudoephedrine glycylglycinamide and pseudoephedrine were isolated. This probably is a result of the combination of two molecules of the O,N-dianion **2.39**, or by nucleophilic attack of the trianion **2.42** on the O,N-dianion **2.39**.

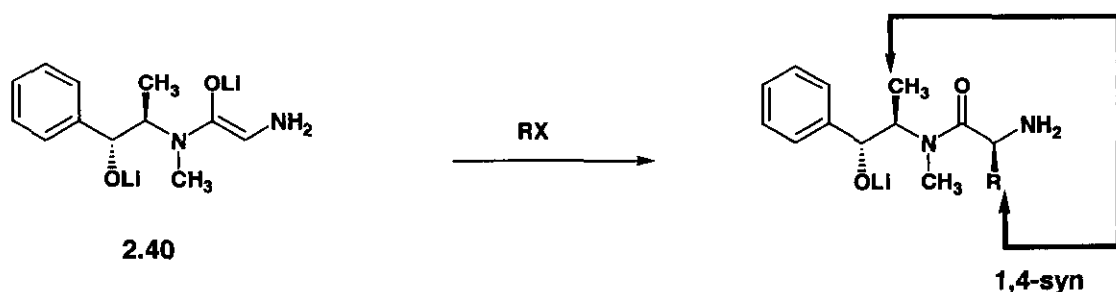


Myers suggested that this problem can be entirely avoided by using 1.95 equiv. of LDA and proposed the following protocol: slow, dropwise addition of a solution of lithium diisopropylamide (LDA) (1.95 equiv.) in THF to a slurry of **2.36** (1 equiv.) and anhydrous lithium chloride (6.00 equiv.) in THF at 0°C. He has shown that the use of 1.95 equiv. of base (LDA) in the enolisation is essential to obtain a high yield of alkylated product. In our

hands, when more than 2 equiv. of base was present, free pseudoephedrine was liberated and the reaction mixture developed a distinct orange colour in contrast to the normal yellow colour of the enolate suspensions prepared with 1.95 equiv. of LDA. Consequently, we used this colour change to indicate when sufficient base was present, generally stopping the addition when the solution was still just yellow, even if this meant using less than the full amount of base calculated from its concentration. Thus, the typical procedure that we adopted involved formation of a slurry of pseudoephedrine glycinamide (1 equiv.) and flame dried lithium chloride (6 equiv.) at 0°C followed by slow addition of LDA at 0°C, and then after 30 min of stirring at 0°C, by the addition of a solution of haloalkane (1.1-1.2 equiv.) in THF.

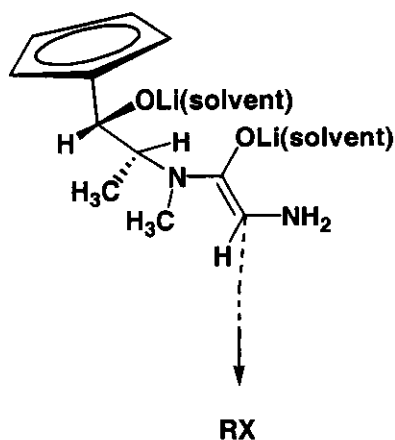
2.2.1.3 Alkylation of pseudoephedrine glycinamide

It has been reported that simple non heterocyclic alkyl halides reacted efficiently and diastereoselectively with the enolate **2.40**. In every case examined the sense of the stereochemical outcome was that outlined in Scheme 2.17.



Scheme 2.17

This stereochemical outcome is the same as that observed in the alkylation of the simple N-acyl pseudoephedrine derivatives. A useful mnemonic for deriving the sense of induction in the alkylation reaction has the electrophile entering from the same face as the methyl group of the pseudoephedrine residue when the (Z)-enolate **2.40** is drawn in a planar extended conformation (Scheme 2.18).

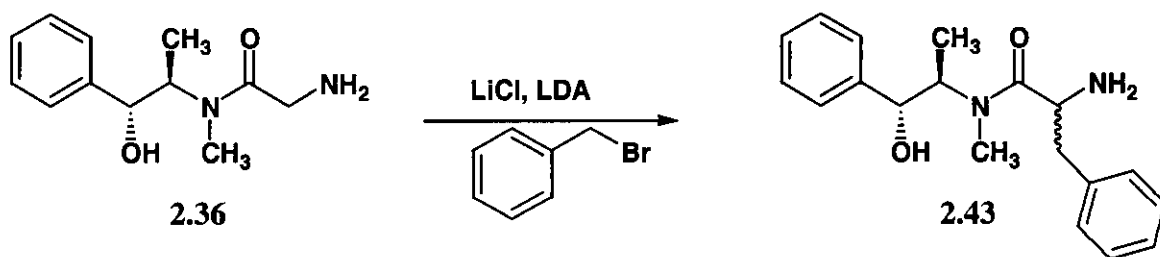


Scheme 2.18

Thus, alkylation of (*S,S*)-pseudoephedrine glycineamide provided (*R*)-amino acids and (*R,R*)-pseudoephedrine glycineamide gave (*S*)-amino acids. In some cases the diastereoselectivity was influenced by the nature of the leaving group; iodoalkanes provided the highest selectivities and chloroalkanes the lowest.

2.2.1.4 Synthesis of phenylalanine

Prior to applying the above method to the synthesis of previously unsynthesised amino acids, we decided to assess the validity of the method by using benzyl bromide as the electrophile (Scheme 2.19). This will ultimately afford the known amino acid, phenylalanine.



Scheme 2.19

Particular care was taken to ensure the use of anhydrous reagents. All the reaction vessels were flame dried and cooled under a positive pressure of argon. Lithium chloride was dried under vacuum for 12 h, then prior to use flame dried and cooled again under a

positive pressure of argon. Using commercial LDA solutions was found to give poor yields in the alkylation step, so we used a freshly prepared solution of LDA made from freshly titrated (against diphenylacetic acid⁷³) *n*-BuLi solution and freshly distilled diisopropylamine. The enolate was prepared by slow addition (30 min) of the LDA solution to a stirred slurry of (*R,R*)-pseudoephedrine glycineamide and LiCl at 0°C. Benzyl bromide was then added to the yellow enolate solution and the mixture stirred at 0°C for 2 h. After work-up and chromatography, compound **2.43** was isolated in 62% yield.

We noticed that, like most tertiary amides, **2.43** exhibited rotational isomerism about the N-C(O) bond and interconversion of isomers was slow on the NMR (¹H and ¹³C) timescale (Figure 2.1 and 2.2). This is shown in particular, by the two N-CH₃ signals at 2.6 and 2.9 ppm in the ¹H spectrum and 27.1 and 30.4 in the ¹³C spectrum. Using the integration of these peaks in the ¹H spectrum, a rotamer ratio of 4 to 1 was found. Unfortunately, a variable temperature NMR experiment (20°C to 100°C) did not show peak coalescence. One further complicating factor was that the ¹H NMR spectrum of **2.43** exhibited the presence of both rotamers and diastereoisomers. Attempts to determine diastereoisomeric ratios by HPLC (reversed phase C18 column) or by chiral GC (Chiral Sil Val column post acetylation) proved unsuccessful as resolution of the peaks corresponding to the two potential diastereoisomers either in HPLC or GC could not be achieved. Compound **2.43** was therefore submitted directly to hydrolysis conditions (Scheme 2.20).

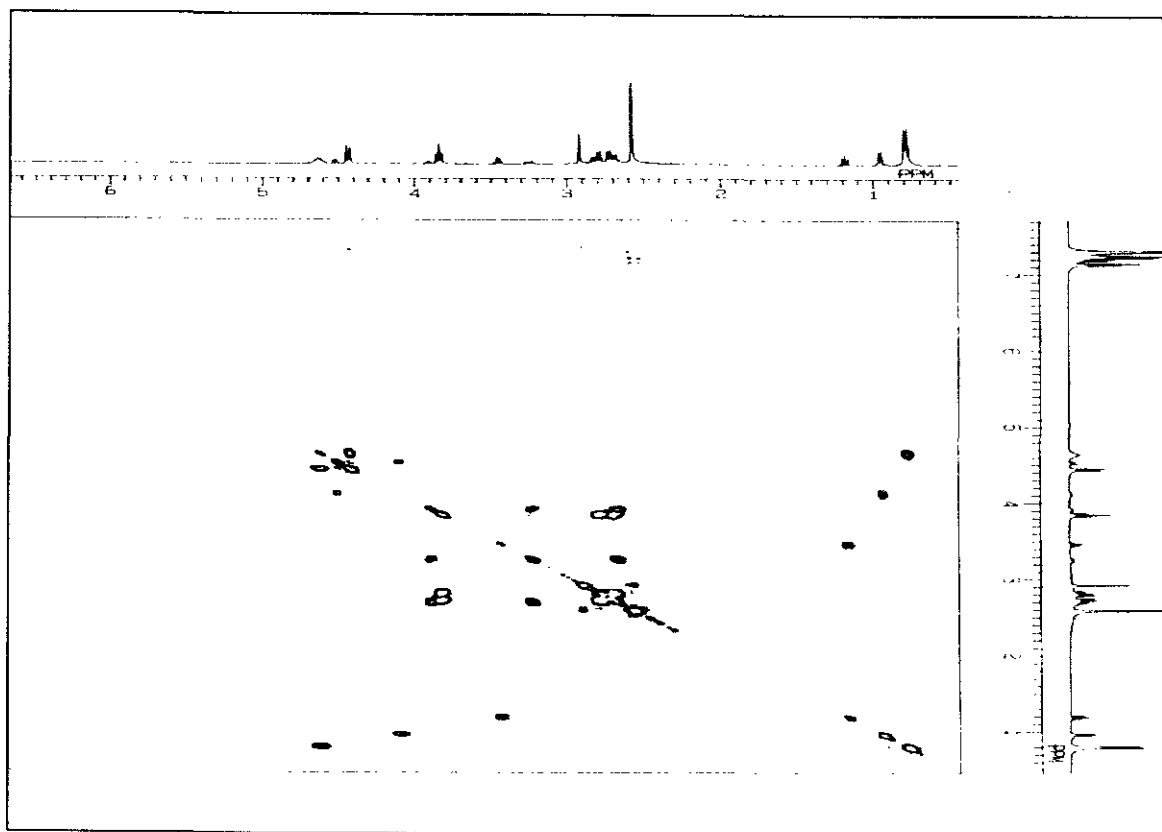


Figure 2.1: $^1\text{H}/^1\text{H}$ COSY of compound 2.43

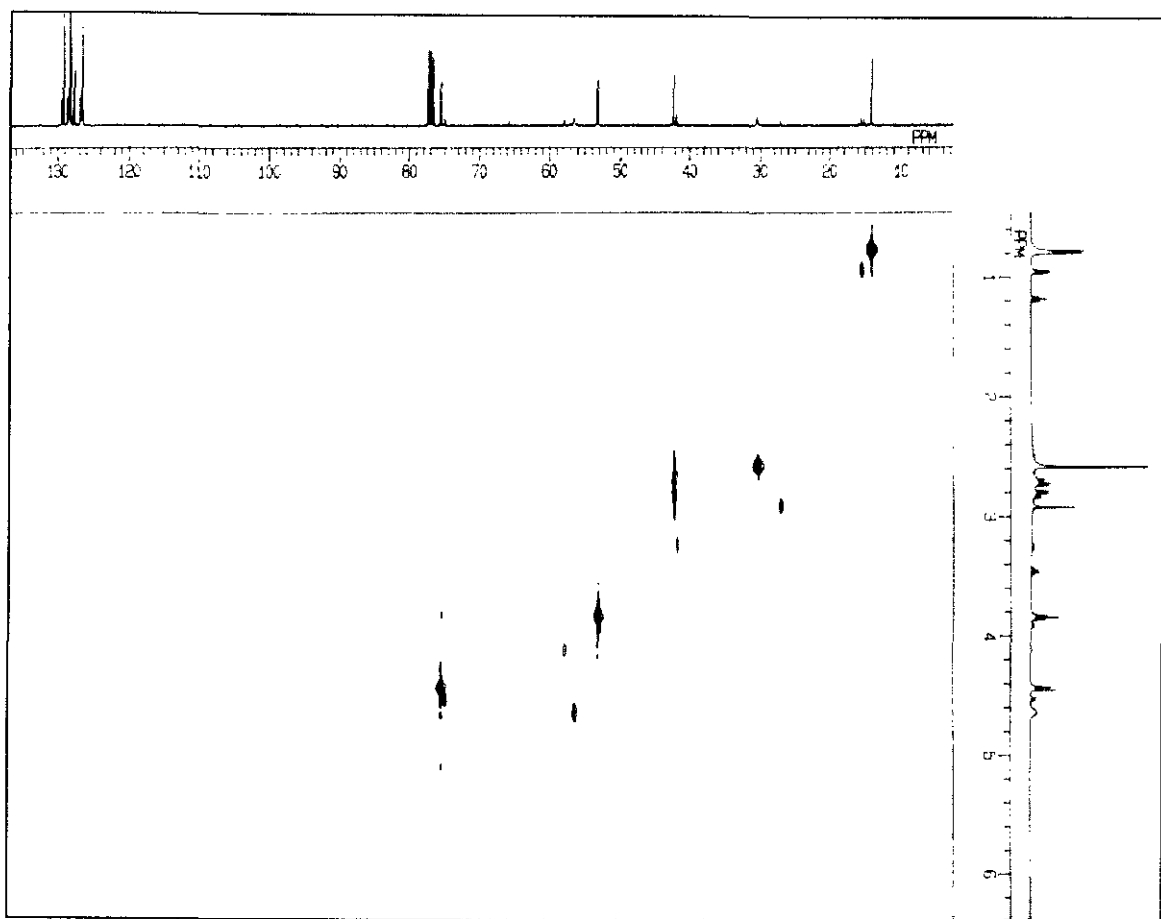
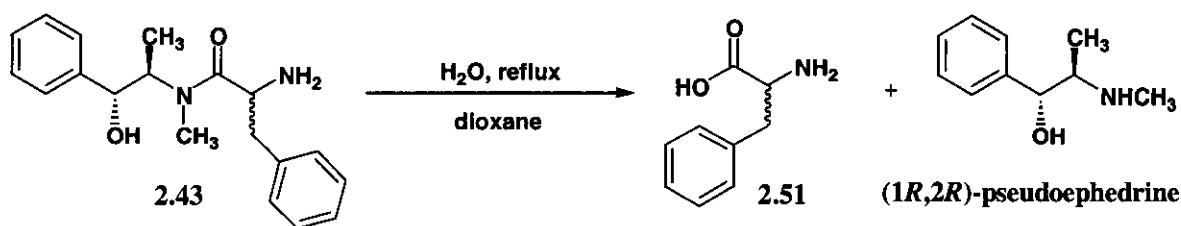


Figure 2.2: $^1\text{H}/^{13}\text{C}$ COSY of compound 2.43



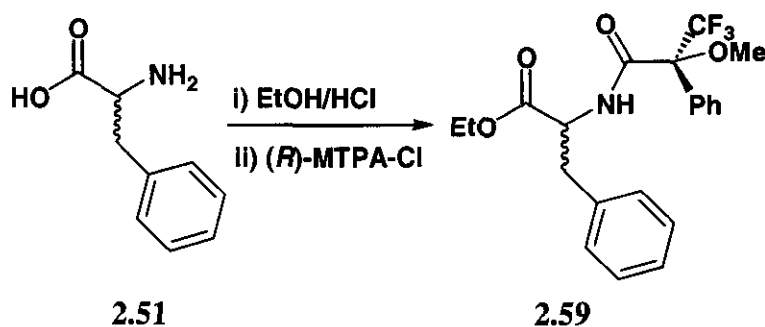
Scheme 2.20

Myers observed that the products of alkylation are easily hydrolysed by refluxing in a slightly alkaline solution. However, we noted that the products resulting from the alkylation displayed some solubility in water and produces alkaline solutions, presumably due to the presence of the free amino group. Therefore, we found that simply heating an aqueous solution of the alkylated product in water/dioxane for 12h led to quantitative hydrolysis to afford the free amino acid together with pseudoephedrine. The latter was removed by extraction with DCM. Evaporation of the aqueous layers and subsequent trituration of the crude amino acid in ethanol served to remove any residual trace of pseudoephedrine. An advantage of using water is that the amino acid product does not require any desalting procedure such as ion exchange chromatography.

Thus, pure phenylalanine **2.51** was isolated in 76% yield after the trituration procedure. Moreover, pure pseudoephedrine was also recovered from the organic phase in 70% yield.

To assess the enantiomeric purity of the phenylalanine so-obtained, we decided to employ the NMR-based method of Mosher⁷⁴. In this, 2-methoxy-2-phenyl-3,3,3-trifluoropropanoic acid (MTPA), or its chloride, MTPA-Cl, of defined stereochemistry is coupled to the compound of unknown configuration to produce diastereoisomeric amides. The method consequently relies on the difference in the ^{19}F NMR chemical shift of the trifluoromethyl group for both diastereoisomers⁷⁵.

The enantiomeric excess (e.e.) analysis was accomplished by esterifying **2.51** using a solution of HCl in ethanol, followed by coupling of the phenylalanine ethyl ester hydrochloride to commercially available (*R*)-MTPA-Cl (Scheme 2.21) and subjecting the product **2.59** to ^{19}F NMR spectroscopy.



Scheme 2.21

The ^{19}F NMR spectrum (Figure 2.3) exhibited two singlets at δ_{F} -69.087 ppm for the major diastereoisomer and δ_{F} -69.141 ppm for the minor diastereoisomer. We related the ratio of these two diastereoisomers (calculated from the integration of each signal) with the e.e. of the original phenylalanine **2.51**. An e.e. of 87 % was determined. Interestingly, Myers has quoted an e.e. of 99% for the same compound⁷².

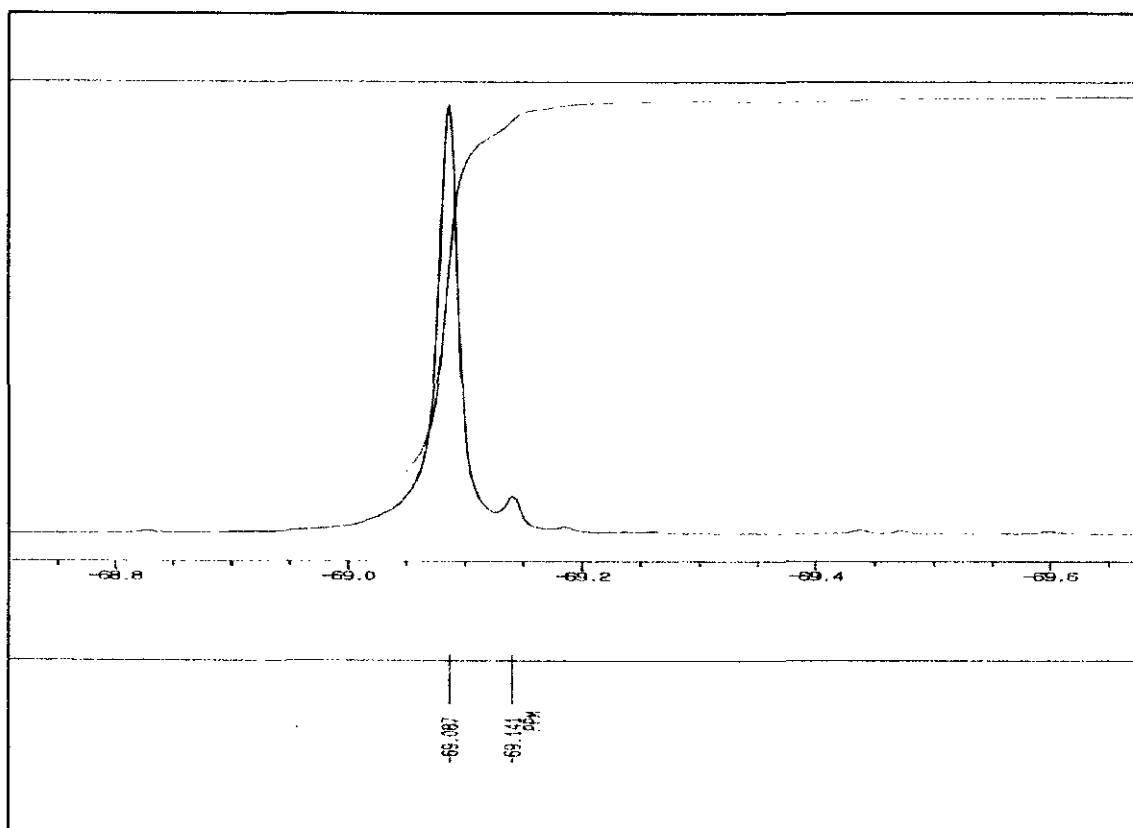


Figure 2.3

To assess whether or not the integrity of the chiral center had been retained during the synthesis, we carried out some test experiments.

First, commercial (*S*)-phenylalanine ethyl ester hydrochloride was coupled to (1*R*,2*R*)-pseudoephedrine using the same conditions as for the coupling with glycine. The resulting amide was then hydrolysed to give phenylalanine, which was subsequently esterified. Coupling to (*R*)-MTPA-Cl and analysis by ^{19}F NMR revealed only one signal at δ_{F} -69.067 ppm (Figure 2.4).

Second, (*R*)-phenylalanine was also coupled to (1*S*,2*S*)-pseudoephedrine, then hydrolysed and coupled to give a Mosher's amide. The ^{19}F NMR spectrum again showed only one singlet. The chemical shift of δ_{F} -67.940 ppm was different from the minor isomer resulting from the alkylation (δ_{F} -69.141 ppm), a difference probably due to the incorrect calibration of the instrument (Figure 2.5).

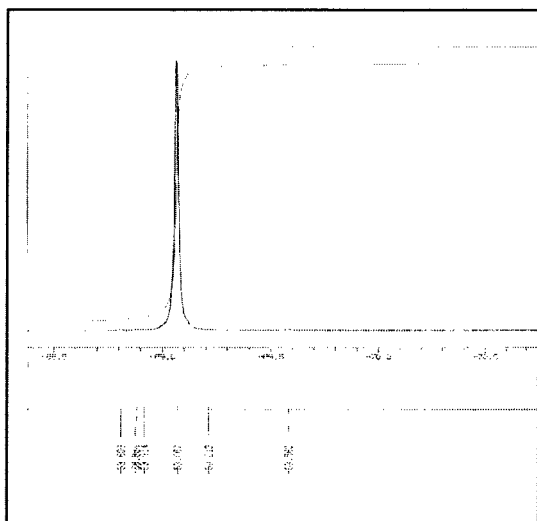


Figure 2.4

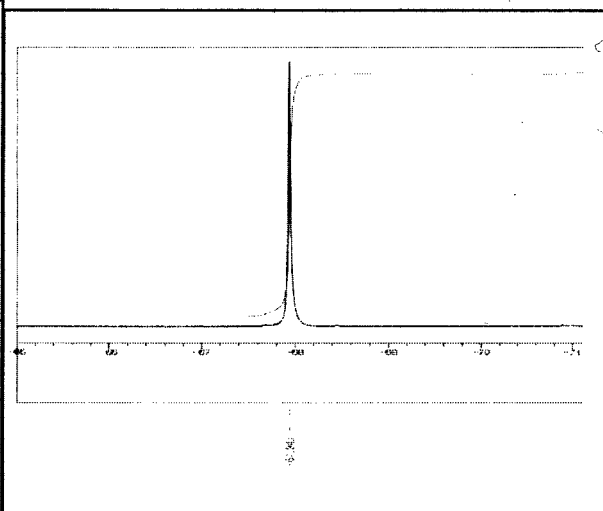
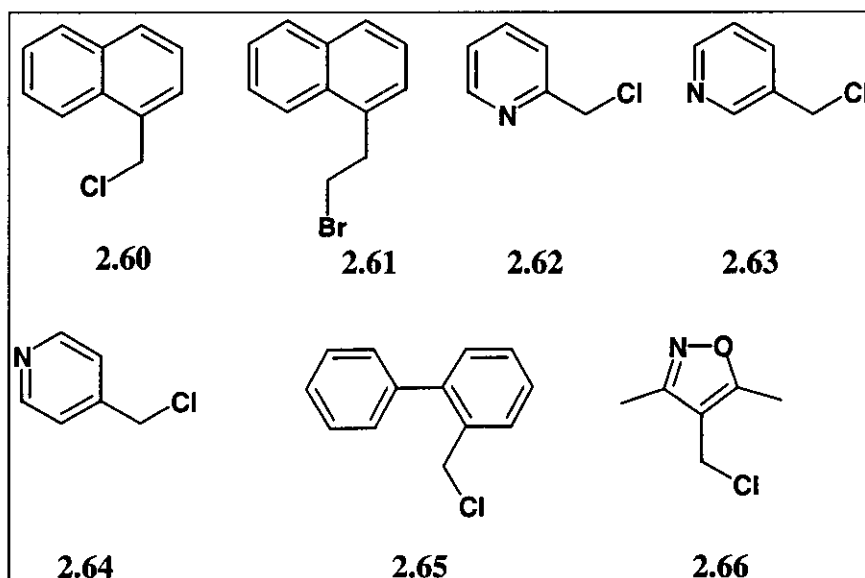


Figure 2.5

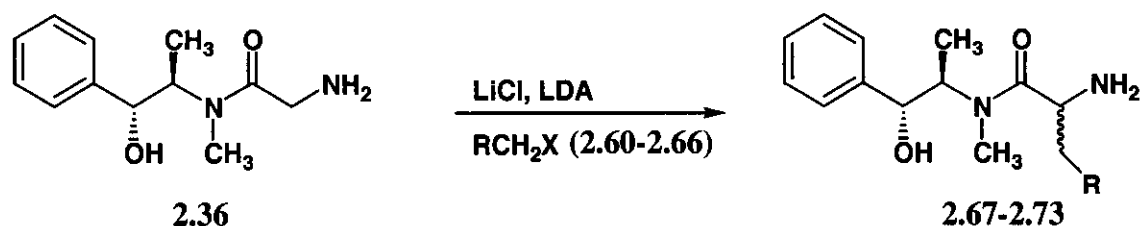
Thus, the integrity of the chiral centre appears not to be compromised in any of the hydrolysis, esterification and coupling steps. We, therefore concluded that the low e.e. obtained for compound **2.51** was only due to moderate diastereoselectivity in the alkylation step. This experiment also verified the finding that (*R,R*)-pseudoephedrine produces (*S*)-amino acids.

2.2.2 Alkylation using other electrophiles

Next, we decided to extend the method to a wider range of electrophiles (**2.60-2.66**). Naphthyl systems **2.60** and **2.61** were chosen because they should have similar reactivity to the benzyl bromide used to test the method. Potentially, amino acids containing such a ring system could serve as intercalating agents. The pyridyl systems **2.62-2.64** are also commercially available and the corresponding amino acids could mimic histidine, for example. Electrophiles **2.65** and **2.66** are also commercially available.



The electrophiles were submitted to the alkylation conditions described above for benzyl bromide, and using (1*R*,2*R*)-pseudoephedrine glycineamide to try and produce (*S*)-amino acids (Scheme 2.22).



Scheme 2.22

The results of the alkylation reactions are displayed in the table shown below (Table 2.1).

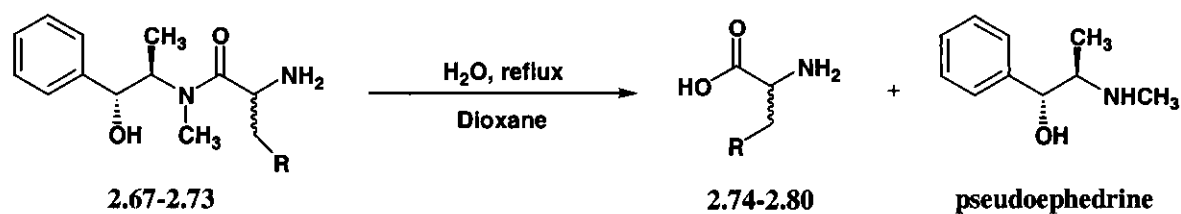
Electrophile	Alkylated product	Yield (%)	Amino acid	Yield (%)	Pseudoephedrine recovered
Benzyl bromide	2.43	62	2.51	76	70
2.60	2.67	61	2.74	76	50
2.61	2.68	33	2.75	74	58
2.62	2.69	62*	2.76	59	
2.63	2.70	55*	2.77	49	
2.64	2.71	36*	2.78	40	
2.65	2.72	68	2.79	48	78
2.66	2.73	97	2.80	59	62

* crude yield

Table 2.1 Product yields from the alkylation of pseudoephedrine glycineamide and from the hydrolysis of the alkylated products.

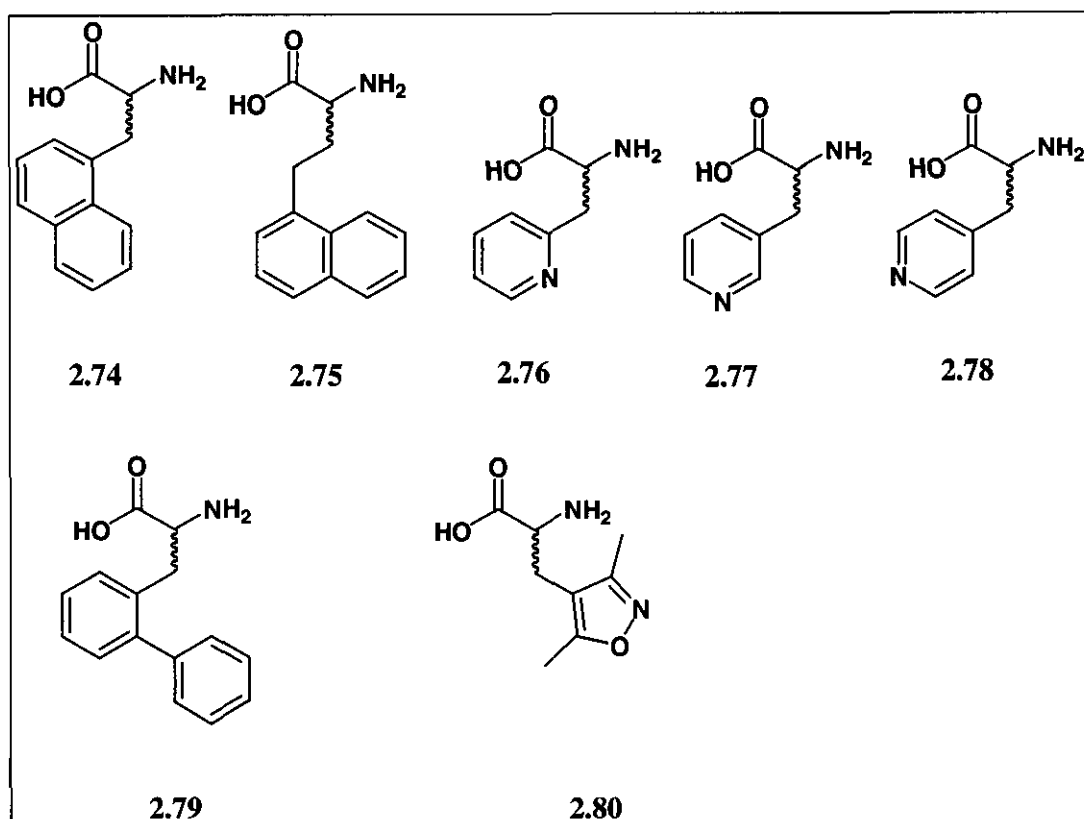
The alkylation reaction proceeded successfully for all the electrophiles selected; in moderate yield for electrophiles **2.60-2.65** (33% to 68%), and in nearly quantitative yield (97%) for the isoxazole electrophile **2.66**. In general, these compounds were sticky gums that could not be crystallised. For the pyridyl series the alkylated products could not be isolated in pure form for spectroscopic characterisation. Indeed, for this series we noted that the starting electrophiles rapidly decomposed both after neutralising the hydrochloride salt with triethylamine and when THF was removed to concentrate the solution prior to alkylation. Consequently, we decided to subject the alkylated products to hydrolysis directly without further purification.

2.2.3 The unusual amino acids



Scheme 2.23

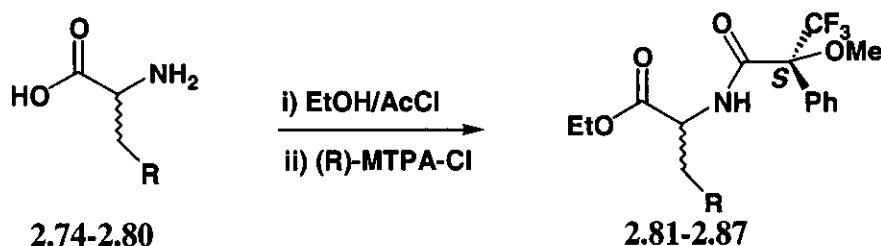
A significant advantage of hydrolysing the alkylated products in an aqueous medium was that the free amino acid was retained in the aqueous phase while the pseudoephedrine co-product could be extracted into DCM. Thus, the desired amino acids were obtained by heating the alkylated products **2.67-2.73** (dissolved in minimal amount of dioxane) at reflux in water for 12 h (Scheme 2.23). Reactions were monitored by HPLC and reached completion after 12 h. A simple extraction with dichloromethane ensured removal of the chiral auxiliary. Further purification was achieved by trituration of the aqueous phase with ethanol to remove any residual pseudoephedrine. In our hands, this procedure successfully provided the desired amino acids **2.74-2.80** with good purity and in moderate yield (40-76%) (Table 2.1).



It is worth mentioning that this hydrolysis procedure helped in the purification of the pyridyl amino acids **2.76-2.78**. However, it was noticed that the pyridyl amino acids were somewhat soluble in ethanol, which may account for lower yields obtained for these compounds.

2.2.4 Enantiomeric purity determination

The amino acids were esterified and converted into their corresponding hydrochloride salt using acetyl chloride in ethanol (which generates HCl *in situ*). The coupling of the amino acids **2.74-2.80** to (*R*)-MTPA-Cl was accomplished in dichloromethane in the presence of an excess of base (Scheme 2.24). The absolute configuration of the chiral centre of a Mosher amide is of course identical with that of the Mosher acid chloride. However, the Cahn-Ingold-Prelog⁷⁶ descriptor changes because COCl has higher priority than CF in the chloride but CON has lower priority than CF in the amide.



Scheme 2.24

The crude mixtures **2.81-2.87** so-obtained were analysed by ^{19}F NMR. Each revealed the presence of two singlets corresponding to the two diastereoisomeric products. The diastereoisomeric excess (d.e.) for each amino acid was calculated using the integration traces for these signals. (see appendix). Again, the e.e. for each amino acid can be equated with these d.e. values (Table 2.2). These results represent the best e.e. values from several reactions carried out for each electrophile.

Amino acid	Mosher's amide	e.e. (%)
2.74	2.81	87
2.75	2.82	61
2.76	2.83	10
2.77	2.84	74
2.78	2.85	68
2.79	2.86	74
2.80	2.87	74

Table 2.2 Enantiomeric excesses determined for amino acids 2.74-2.80

Unfortunately, these results were found to be very difficult to reproduce. One factor that may contribute to this is the determination of the end point for the addition of $n\text{-BuLi}$. Another is the physical state of the LiCl . It was found that drying lithium chloride under vacuum for 12 h and further flame drying had an effect on the yields obtained (higher) and also seemed to raise the enantiomeric excess of the amino acids. These conditions could not be identically applied in all cases.

Nonetheless, several unusual interesting amino acids were produced with moderate e.e. using pseudoephedrine as a chiral auxiliary. With this relative success in mind, we decided

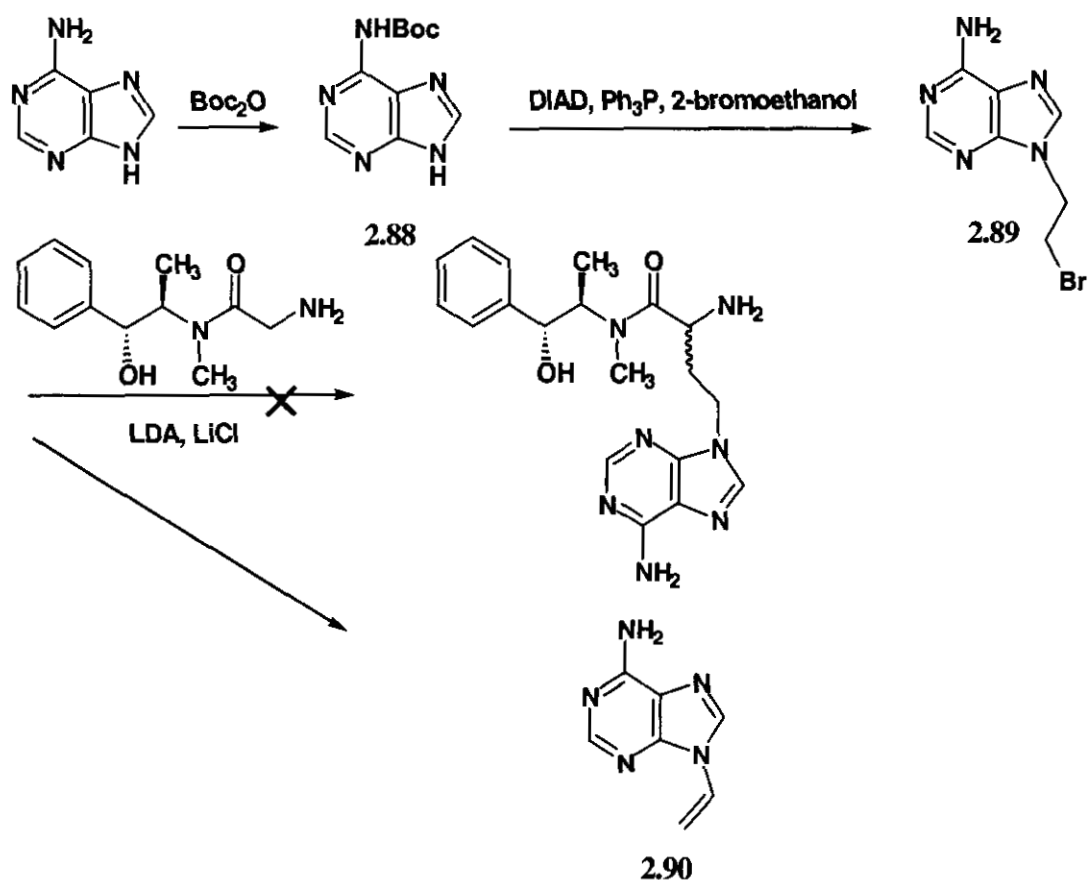
to extend further the use of pseudoephedrine as a chiral auxiliary to more complex heterocyclic amino acids. Amino acids bearing nucleic acid bases in their side chain seemed to be more valuable targets.

2.2.5 Limitation of the enolate method

We envisaged that the same methodology could be used for the synthesis of these amino acids bearing a nucleobase in the side chain.

2.2.5.1 *N*9-(2-Bromoethyl)-*N*6-aminopurine as electrophile

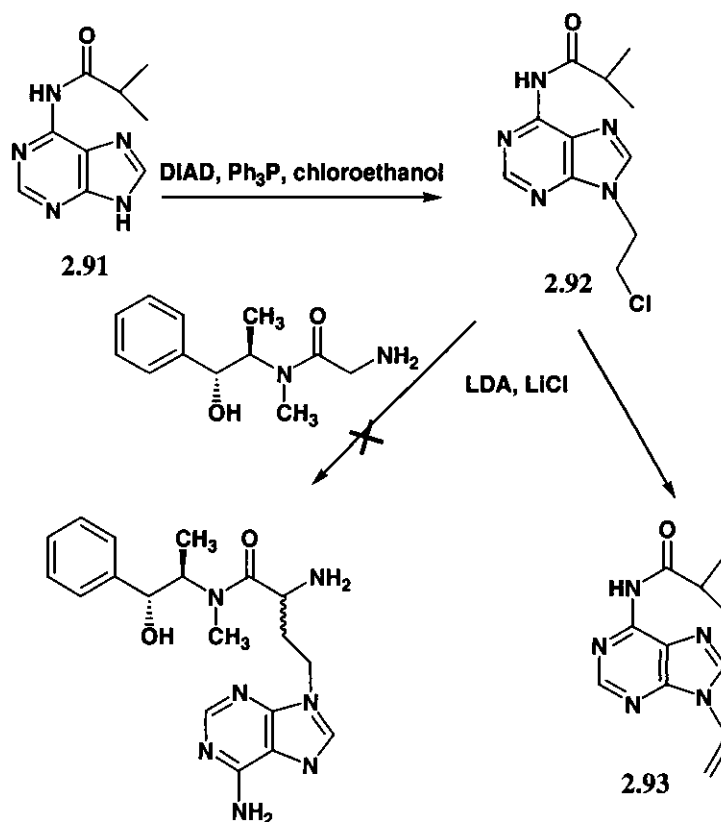
Commercially available *N*6-aminopurine (adenine) was chosen as the precursor for the synthesis of the halopurine electrophile **2.89**; this required the use of protecting groups (Scheme 2.25). We decided to use a non-base sensitive protecting group to avoid deprotection by LDA in the alkylation step. Adenine was Boc-protected selectively at N-6 in 75% yield using Boc-anhydride (1 equiv.). *N*6-Boc-Adenine **2.88** was then alkylated at N-9 in 21% yield under Mitsunobu conditions using 2-bromoethanol with diisopropyl azodicarboxylate and triphenylphosphine to give **2.89**. Surprisingly, the Boc-group was lost during the Mitsunobu reaction, presumably upon product purification on the acidic silica gel. The desired purine electrophile **2.89** was submitted to alkylation in the usual way using (1*R*,2*R*)-pseudoephedrine glycineamide. However, the desired alkylated product was not isolated; rather a mixture containing the elimination product **2.90** (77% spectroscopic yield) and the starting bromide **2.89** was recovered instead. Clearly, the strong base LDA ($pK_a > 30$) was able to deprotonate the acidic proton α to N-9 therefore promoting the elimination process. However, the presence of the adjacent electronegative ring N atom must also enhance the acidity of the α -proton given that we have successfully employed 1-(2-bromoethyl)naphthalene **2.61** in this reaction.



Scheme 2.25

2.2.5.2 N⁹-(2-Chloroethyl)-N⁶-(2-methylpropanoyl)adenine as electrophile

We decided to examine whether or not a chloroethyl electrophile would enhance alkylation over elimination. A 2-methyl propanoyl protecting group at N-6⁷⁷ was also used in lieu of the Boc group (Scheme 2.26).



Scheme 2.26

*N*9-(2-Chloroethyl)-*N*6-(2-methylpropanoyl)aminopurine **2.92** was synthesised in 71% yield according to a literature method⁷⁷ (discussed in detail in Chapter 3) and subjected to the conditions for the alkylation of pseudoephedrine glycine amide. However, once again only the elimination product **2.93** together with the starting material **2.92**, was isolated in 77% (spectroscopic yield).

2.2.6 Conclusion

The pseudoephedrine glycine enolate method has been successfully extended to the synthesis of seven unusual heterocyclic amino-acids in good yield and moderate enantiomeric excess. However, despite significant effort, the e.e. of the new amino-acids were never as high as those claimed for Myers examples. It seems that stringently anhydrous conditions, together with less than 2.0 equiv. of LDA, are required for the

enolisation/alkylation step. Moreover, reproducibility for a given reaction (using exactly 1.95 equiv. of LDA) was difficult to achieve.

A serious disadvantage of the enolate route was that it could not be used to access heterocyclic amino acids bearing a nucleobase in the side chain. Here, competition between substitution and elimination completely favours the latter.

Therefore, a new route using milder conditions was required if the synthesis of amino acids having nucleobases in the side chain was to be achieved. This new methodology, together with the results obtained, are discussed in the next chapter.

CHAPTER 3

A RADICAL APPROACH

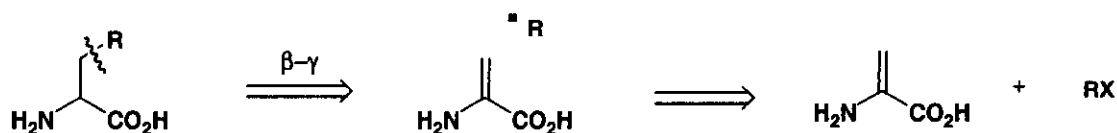
3.1 INTRODUCTION

It has been shown in Chapter 2 that in the application of the enolate approach to the synthesis of unnatural amino acids, we encountered some limitations when using base sensitive electrophiles where elimination could occur. To reach our goal of incorporating complex heterocycles into the side chain, a milder approach was required. It was anticipated that a radical approach would be more suitable. Indeed, over the last decade or so, chemists have exploited radical reactions to achieve transformations in a controlled manner, in good yield and with high regio- and stereoselectivity. Very often the reagents and reaction conditions used in free radical reactions are more compatible with the functional groups present (even without protection) and the stability of the compounds involved. This chapter will first extend the disconnection outlined in the introduction related to the formation of the C-C bond using a radical methodology (radical alanine synthetic equivalent), and will thus provide a general overview of the chemistry of radicals using both non-optically-active and optically-active dehydroalanine synthetic equivalents. We will then describe and demonstrate how we have successfully utilised an oxazolidinone derivative for the synthesis of optically active amino acids bearing nucleic acid bases (purines and pyrimidines) in their side chain.

3.1.1 Non-optically active dehydroalanine

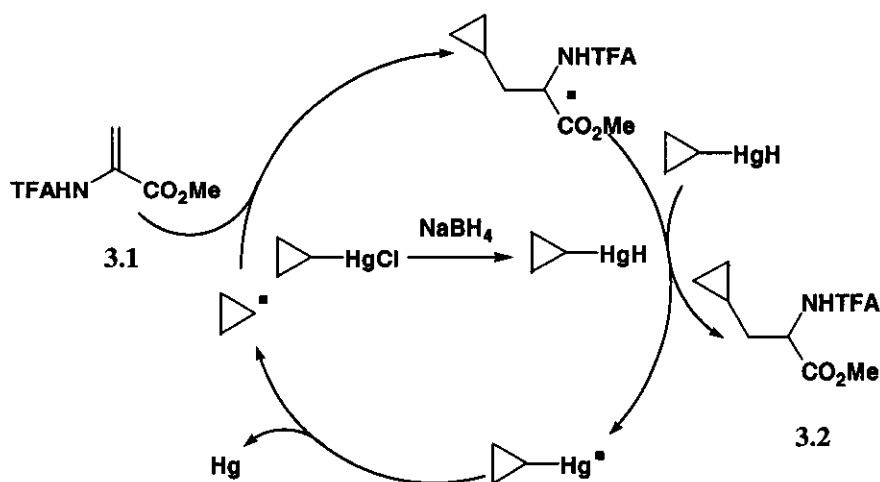
Most intermolecular radical reactions of amino acid derivatives generate an α -centred radical, presumably as a result of the particular stability of this species. Many examples involve the introduction of an amino acid side chain, with formation of a carbon-carbon bond. If we disconnect the C $_{\beta}$ -C $_{\gamma}$ bond, then we can conceive of a reaction involving

dehydroalanine (or equivalent) and a radical that could come from fragmentation of a C-X bond (Scheme 3.1).



Scheme 3.1

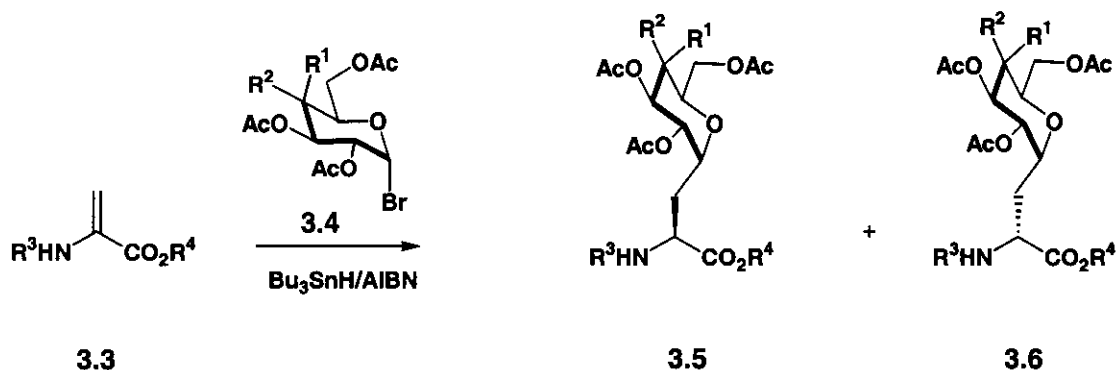
Indeed, Crich⁷⁸ has reported a mild method for the synthesis of α -amino acids by conjugate addition of free radicals to a protected dehydroalanine derivative. *N*-Trifluoroacetyl amino acid methyl ester **3.2** were prepared by the addition of a cyclopropyl radical to *N*-trifluoroacetyldehydroalanine methyl ester **3.1**. The choice of trifluoroacetyl as the *N*-protecting group was guided by a desire to minimise any stabilization of the adduct radical, therefore promoting good chain-carrying properties and reducing dimerisation, as well as by the ease of introduction and removal of this group.



Scheme 3.2

The method proved applicable to the addition of primary, secondary as well as tertiary radicals, with moderate to good yields (30-85%) being achieved. Using this route, Crich was able to prepare the antifungal amino acid derived from **3.2** and isolated from the mushroom *Amanita virginoides*⁷⁹.

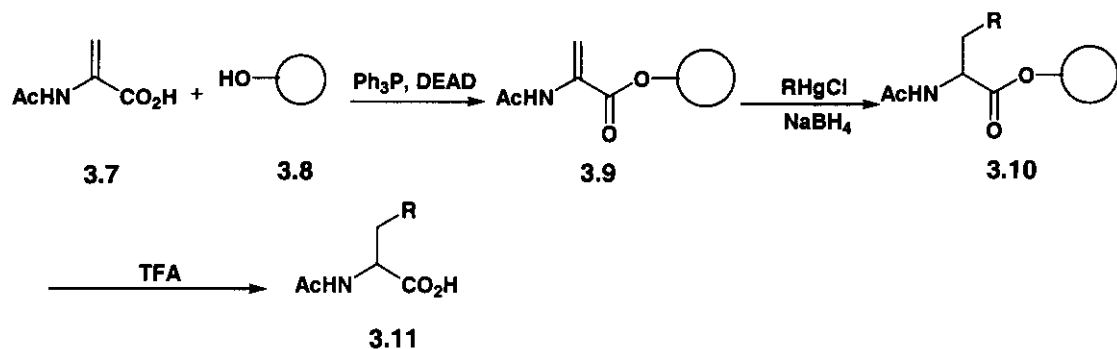
A similar strategy was used by Kessler⁸⁰ to produce C-glycopeptides in yields up to 73% (Scheme 3.3).



Scheme 3.3

The sugar dehalogenated at C1 was isolated as a by-product. Interestingly, the C-glycosyl amino acid products were exclusively (>97%) of α -configuration at the anomeric centre of the sugar. In contrast to this high stereoselectivity at the sugar, final hydrogen transfer to C2 of the glycine backbone of the amino acid yielded mixtures of epimers **3.5** and **3.6**. The possibility of increasing the diastereoselectivity was examined through chirality in the dehydro-amino acid building block without any real success.

Martinez has extended the method to the use of polymer supports⁸¹, with the first synthesis of N-acetyl- α -amino acids by the addition of radicals to polymer supported 2-acetamidodehydroalanine (Scheme 3.4). Martinez outlined a three-step strategy. The amino acid **3.7** was anchored onto Wang resin (4-alkoxybenzyl alcohol polystyrene, **3.8**) through the carboxylic acid function using a Mitsunobu method. Generation of radicals was accomplished using Giese's mercury method⁸² in which a dropwise addition of an excess of sodium borohydride to a mixture of compound **3.9** and alkylmercury chloride generated the adduct **3.10**. The product was then cleaved from the solid support using TFA, to yield the desired N-acetylamino acids **3.11**. Of course, one advantage of this approach is that the excess reagents can easily be removed by washing the resin.



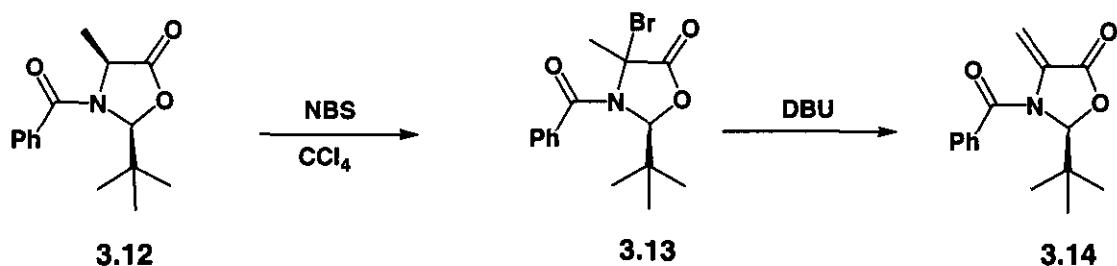
Scheme 3.4

3.1.2 Oxazolidin-5-one as chiral dehydroalanine equivalent

The synthesis of optically active amino acids using a radical method can be achieved by two separate approaches. The first is to use a chiral centre already present in the starting material and then generate a radical in the side chain; the second is to create the chiral centre at the α -carbon by stereoselective addition of a radical onto a dehydroalanine equivalent. In either method there is a need to direct the stereochemistry by H-atom capture on the carbon centred radical by steric influence of a neighbouring chiral center. One way of achieving this is normal asymmetric induction, another is the self-regeneration of chiral centres⁸³. In the latter, a chiral centre, subsequently destroyed, is used to induce a new one, then this new chiral centre is used to induce chirality at the original centre.

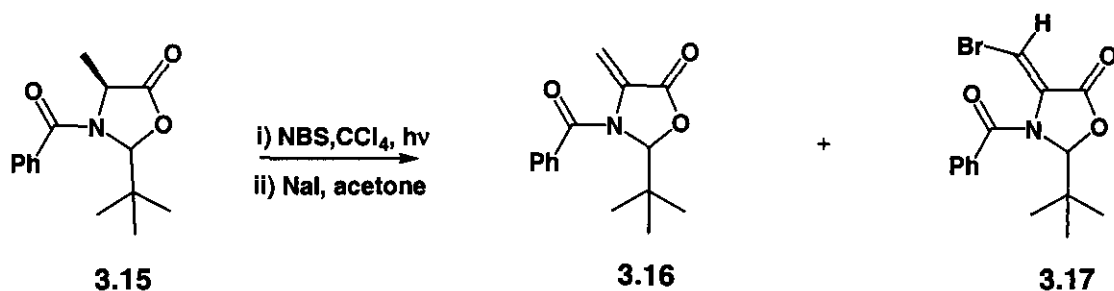
The oxazolidinone template is the most important tool for radical addition to form a C-C bond. In this section, first the synthesis of suitable oxazolidinones will be discussed and, second, recent successful applications of these to the synthesis of amino acids *via* radical methods will be reviewed.

Oxazolidinone **3.12**, made from (*S*)-alanine, afforded the bromo derivative **3.13** by radical bromination using NBS, and subsequent dehydrohalogenation with DBU gave the derivative **3.14** (Scheme 3.5)⁸⁴.



Scheme 3.5

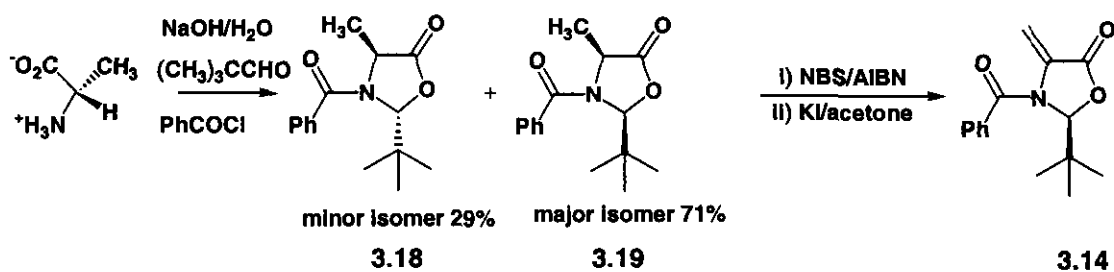
Later, Beckwith reported that the above procedure gave mixtures (Scheme 3.6) and he therefore devised an alternative method from which both enantiomers of **3.16** could be accessed in high enantiomeric purity⁸⁵.



Scheme 3.6

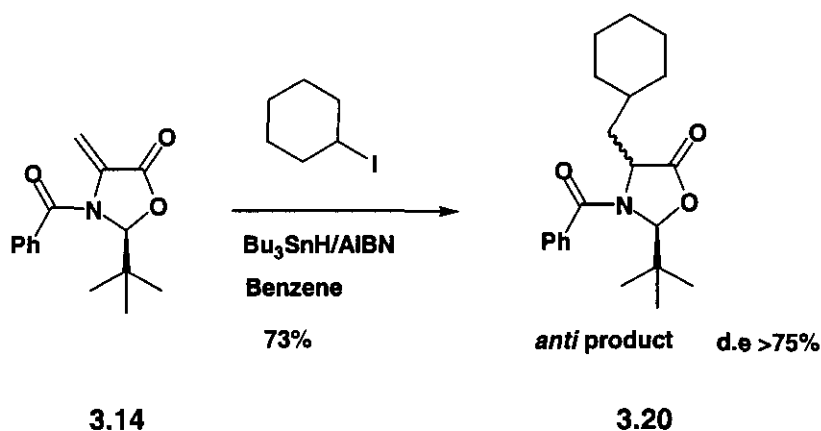
Thus, under photolytic conditions at ambient temperature using stringently purified NBS, followed by treatment with NaI in acetone, the formation of the vinyl bromide **3.17** was suppressed to below 5%.

This approach was extended by Crossley and Tansey to prepare the two diastereoisomeric oxazolidinones **3.18** and **3.19** and subsequently the enantiomer **3.14** (Scheme 3.7)⁸⁶.



Scheme 3.7

The first radical addition onto the oxazolidinone dehydroalanine equivalent **3.14** was accomplished by Beckwith and Chai⁸⁷. The oxazolidinone **3.14** and iodocyclohexane in benzene were irradiated with UV light at room temperature while tributyltin hydride and AIBN in benzene were added from a syringe pump; this gave a mixture of the two diastereoisomers **3.20** resulting from addition of the cyclohexyl radical onto the alkene acceptor of the dehydroalanine equivalent (Scheme 3.8).



Scheme 3.8

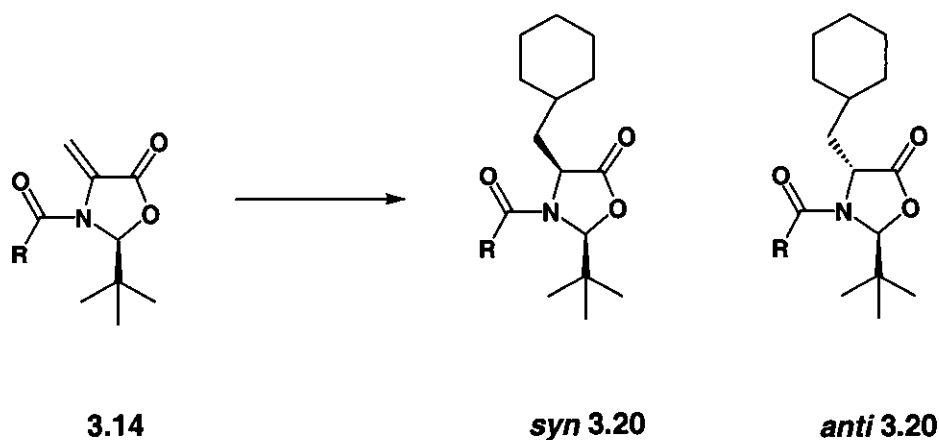
Similarly, the oxazolidinone **3.14** was treated with various iodoalkanes and tributyltin hydride yielding the *anti* diastereoisomers (assigned on the basis of n.O.e. experiments) as the major products (Table 3.1).

Iodoalkane	Major isomer	%yield	%d.e.
MeI	<i>Anti</i>	60	42
PhCH ₂ I	<i>Anti</i>	71	46
^t BuI	<i>Anti</i>	70	75

Table 3.1

In a later publication, Beckwith showed that the diastereoselectivity of the radical addition depends on the nature of the addend radical and on the N-protecting group⁸⁸. Typically, N-benzoyloxazolidinones **3.14** (R=Ph) gave the *anti* products **3.20**, whereas, the carbamates

(R=PhCH₂O, MeO, PhO) gave the *syn* products **3.20** with very high diastereoselectivity (Scheme 3.9).

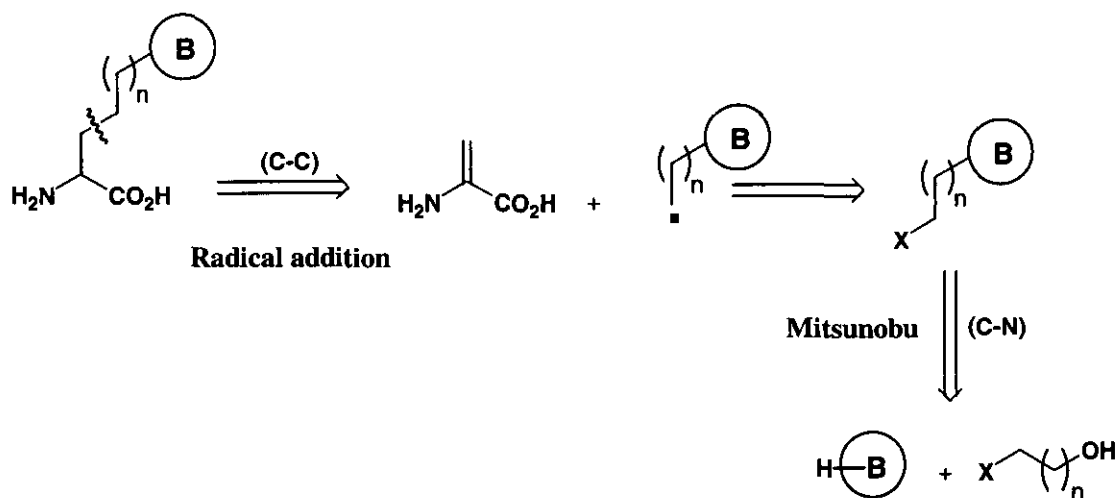


Scheme 3.9

We describe in the next section our findings on the successful application of an oxazolidin-5-one to the synthesis of a range of α -amino acids containing different nucleic acid bases in their side chains.

3.2 Results and discussion

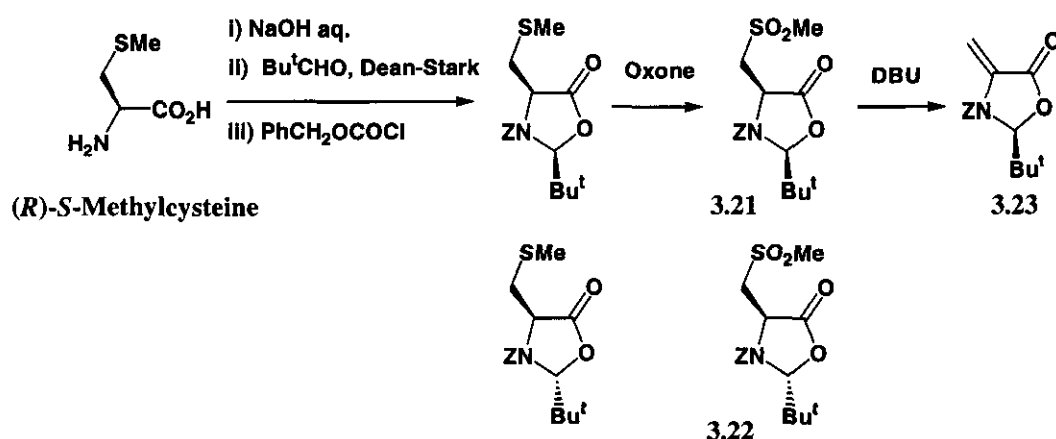
We proposed the disconnection strategy shown in Scheme 3.10, i.e. disconnection of the C(β)-C(γ) bond. This C(β)-C(γ) identifies conjugate radical addition of a preformed radical containing the nucleic acid base onto a dehydroalanine acceptor as the appropriate C-C bond-forming reaction. The nucleic acid radical should be accessible from a haloalkylnucleobase, and the haloalkylnucleobases themselves *via* C-N bond formation using a Mitsunobu procedure involving the nucleobases and commercially available haloalcohols. One advantage of this strategy is that the distance between the glycine backbone and the nucleobase can be varied by the choice of an appropriate haloalcohol. In adopting this strategy, we decided to synthesise a chiral dehydroalanine equivalent so that we could achieve stereoselective conjugate radical addition.



Scheme 3.10

3.2.1 Synthesis of the chiral dehydroalanine equivalent

The chiral dehydroalanine equivalent was synthesised from (*R*)-*S*-methylcysteine, an inexpensive, readily available amino acid, in four steps by adaptation of a published sequence to the *N*-benzoyl analogue (Scheme 3.11)⁸⁹.



Scheme 3.11

The amino acid (*R*)-*S*-methylcysteine was stirred with one equivalent of aqueous sodium hydroxide to give the corresponding carboxylate. The water was removed and the salt dried

under vacuum. 2,2-Dimethylpropanal was then added and the mixture refluxed in hexane with azeotropic removal of water. The resulting Schiff base was treated with benzyl chloroformate to effect cyclisation. Attempts to purify the two diastereoisomeric methylthiomethyl compounds resulted in significant loss of material (these compounds proved inseparable). Indeed, it was found that the methylthiomethyl compounds rapidly oxidised on silica gel or in air to the corresponding sulfones **3.21** and **3.22**. The diastereoisomeric ratio of *syn/anti* methylthiomethyl products could be measured by determining the ratio of the integrals for the SMe singlets at δ 2.10 ppm (major diastereoisomer) and δ 2.02 ppm (minor isomer) prior to oxidation. Typically, a ratio of *ca.* 8 to 1 was found.

We therefore decided to carry out only a rapid extraction procedure to remove any excess benzyl chloroformate and to perform the next oxidation step, directly on the semi-crude material. Oxidation was achieved by dropwise addition of a solution of the diastereoisomeric methylthiomethyl compounds in acetonitrile to an aqueous solution of Oxone[®]. The reaction was monitored by ¹H NMR spectroscopy using the SMe peaks of the thioether starting material and sulfone product. The sulfones were extracted once the singlets at δ 2.10 ppm and δ 2.02 ppm corresponding to the thioether had disappeared and been converted into the singlets at δ 2.87 (minor diastereoisomer) and δ 3.09 ppm (major diastereoisomer) corresponding to the SO₂Me of the sulfones **3.21** and **3.22**. The *syn/anti* ratio of the two diastereoisomeric sulfones was determined by measuring the ratio of integrals for these two SO₂Me peaks. As expected, and confirming our findings for the methylthiomethyl compound diastereoisomers, we found a ratio of *ca.* 7 to 1. This ratio did not vary significantly from experiment to experiment, and did not depend on the scale of the reaction. The two diastereoisomeric sulfones were easily separated by column chromatography on silica gel. The overall yield of the sulfones was *ca.* 57%. We were also able to crystallise the major diastereoisomer from hexane to further ensure diastereoisomeric purity.

To determine the relative stereochemistry at the C2 and C4 positions of the oxazolidinone ring in the sulfones, n.O.e. studies were performed. The results are shown in Table 3.2.

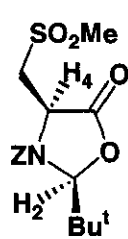
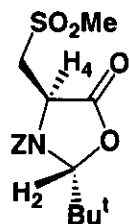
	Signal irradiated	Signal enhanced
	$\underline{\text{CH}}_2\text{SO}_2\text{Me}$	Bu^t (2.18%)
	Bu^t	$\underline{\text{CH}}_2\text{SO}_2\text{Me}$ (1.12%)
	H_2	H_4 (1.18%), Bu^t (6.88%)
	H_4	H_2 (0.92%), $\underline{\text{CH}}_2\text{SO}_2\text{Me}$ (4.58%)

Table 3.2

Irradiation of the H_4 proton gave a small enhancement of the H_2 proton (0.92%) but no enhancement of the *tert*-butyl group. Irradiation of the H_2 proton gave also a small enhancement of H_4 (1.18%) but no enhancement of the $\underline{\text{CH}}_2\text{SO}_2\text{Me}$ protons. Moreover, irradiation of the *tert*-Bu group gave an enhancement of the $\underline{\text{CH}}_2\text{SO}_2\text{Me}$ (1.12%). Irradiation of the $\underline{\text{CH}}_2\text{SO}_2\text{Me}$ gave also an enhancement of the *tert*-Bu group (2.18%).

These mutual enhancements, despite being small, showed that the major isomer obtained was *syn*. This result was in accord with that of Pyne who found that under similar conditions other common α -amino acids (e.g. alanine) gave mixtures of *syn* and *anti* oxazolidin-5-ones in which the *syn* isomer was predominant⁸⁹.

Similar n.O.e experiments were also conducted with the minor sulfone diastereoisomer 3.22 (Table 3.3).

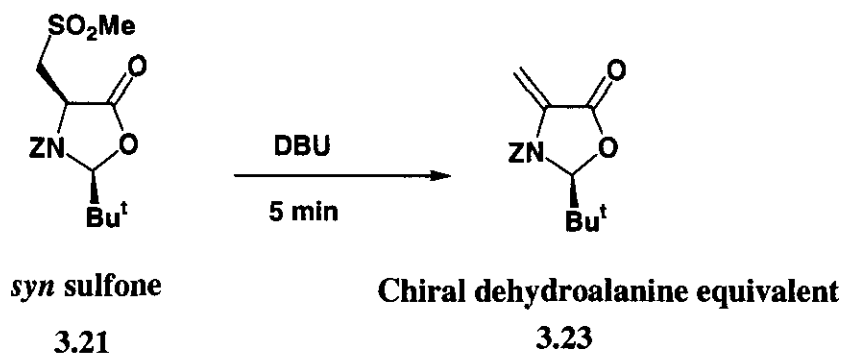


Signal irradiated	Signal enhanced
$\text{CH}_2\text{SO}_2\text{Me}$	H_4 (14%)
Bu^t	H_2 (1.94%), H_4 (0.55%)
H_2	Bu^t (8.47%)
H_4	Bu^t (2.33%), $\text{CH}_2\text{SO}_2\text{Me}$ (7.41%)

Table 3.3

Irradiation of the *tert*-Bu group gave a weak enhancement of H_4 (0.55%) and, irradiation of H_4 gave an enhancement of *tert*-Bu (2.33%). Unfortunately, there was no enhancement between $\text{CH}_2\text{SO}_2\text{Me}$ and H_2 . Nevertheless, enhancement between H_4 and *tert*-Bu was strong enough to conclude that they were *syn* to each other. In other words, the minor sulfone diastereoisomer **3.22** had *anti* stereochemistry.

The final reaction involved an elimination in the presence of a strong hindered base (Scheme 3.12). DBU was added dropwise to a solution of the *syn*-sulfone **3.21** in dichloromethane at 0°C. In the procedure reported by Pyne and coworkers, similar sulfones were treated with DBU for 30 min to effect the elimination reaction. We found, like Mackay⁹⁰, that the reaction was essentially completed after 5 min and that longer times led to some product decomposition. After a conventional extraction procedure the crude product was passed through a short-path silica column to remove excess unreacted DBU.



Scheme 3.12

The desired chiral template was then further purified by recrystallisation from hexane and obtained in 96% yield. In the ^1H NMR spectrum, the disappearance of the SO_2Me singlet at δ 3.09 ppm and of the $\alpha\text{-CH}$ doublet of doublets at 4.9 ppm, and the appearance of a singlet at δ 5.7 ppm integrating to two protons corresponding to the alkene protons, indicated that we had indeed effected the required elimination to afford the (*S*)-oxazolidinone. The (*R*)- enantiomer would be available either from unnatural (*S*)-*S*-methyrcysteine, or from the *anti*-sulfone.

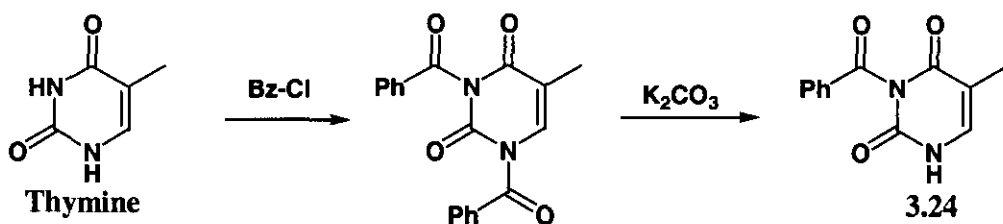
3.2.2 Alkylation of nucleic acid bases

In the past few years, the Mitsunobu reaction has become an important regiospecific method (*N*1 for pyrimidine and *N*9 for purines) for the coupling of haloalcohols with nucleic acid bases under mild conditions. For example, it has recently been demonstrated that *N*3-benzoyluracil and *N*3-benzoylthymine undergo *N*1 alkylation with non-hindered alcohols⁹¹. The *N*1 alkylation of *N*4-benzoylcytosine usually leads to a mixture of *N*1 and *O*2 alkylated products⁹². Nevertheless, it seemed that the Mitsunobu reaction could be used as a general approach to access haloalkyl pyrimidines and purines. In the following sections, we explain how we have used Mitsunobu conditions and appropriate protecting groups to synthesise the desired radical precursors.

3.2.2.1 Synthesis of haloalkylpyrimidines

Synthesis of N3-benzoylthymine

When thymine was stirred with a large excess of benzoyl-chloride (2.2 equiv.) in a mixture of acetonitrile-pyridine at room temperature for 12h (Scheme 3.13), it was converted into the *N1,N3*-dibenzoyl derivative⁹³. The crude diprotected product was treated directly with a solution of potassium carbonate in dioxane-water. Selective *N1* deprotection afforded the *N3*-benzoylated thymine **3.24** containing traces of unreacted thymine. Thymine could be removed by column chromatography on silica gel but routinely the crude material was used directly without any further purification. This reaction was scaled up to 5 g thymine without any major noticeable decrease in yield (67%).



Scheme 3.13

The NMR spectroscopic data for our sample of *N3*-benzoylthymine **3.24** was in accordance with those quoted by Reese⁹³. Thus, the NH signal of our material appeared at δ 11.36 ppm (lit.⁹³ δ 11.2 ppm). In the ^{13}C NMR spectrum, the C-5 carbon of our sample appeared at δ 107.90 ppm (lit.⁹³ δ 107.87 ppm). Our material also gave a satisfactory accurate mass from mass spectroscopic analysis (231.0769 for $C_{12}H_{10}N_2O_3$).

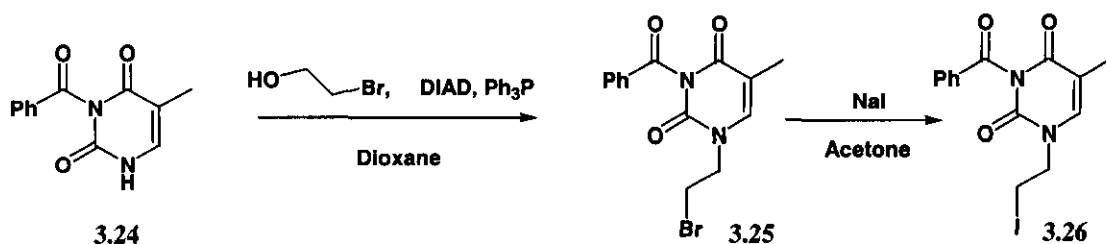
N3-Benzoylthymine **3.24** is known to undergo *N1* alkylation under Mitsunobu conditions. For example, Lucas⁹² has found that cyclopentanol alkylate *N3*-benzoylthymine at *N1*.

We decided to employ the same conditions but using 2-bromoethanol as the alkylating agent.

Synthesis of N3-benzoyl-N1-(2-bromoethyl)thymine and N3-benzoyl-N1-(2-iodoethyl)thymine

N3-Benzoylthymine **3.24** was stirred with triphenylphosphine and 2-bromoethanol in dioxane at 0°C (Scheme 3.14). Since the reaction was exothermic, it was decided to add the diisopropylazodicarboxylate (DIAD) at 0°C via syringe pump over 30 min. It was found that such slow addition increased the yield of the reaction over simple dropwise addition. The reaction was then left to warm up to room temperature and stirred overnight to yield a clear solution.

Purification by column chromatography gave the desired N1 bromoalkylated compound **3.25** as a white solid in 89% yield. It should be noted that no other alkylated compound (e.g. O2 alkylation) was detected upon analysis of the reaction mixture.

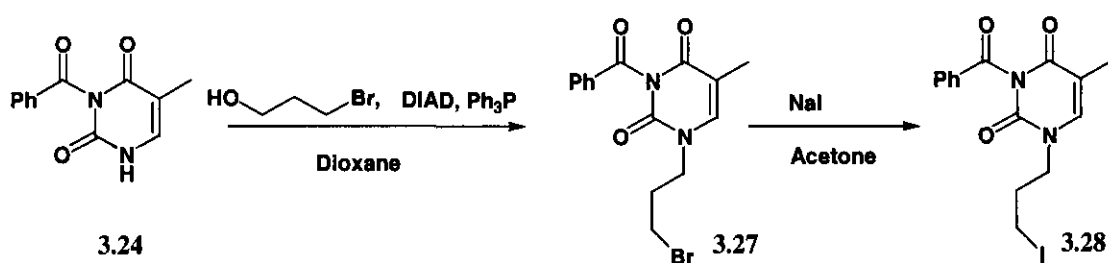


Scheme 3.14

In the course of our studies, these results were supported by Scheiner⁹⁴ who observed only N1 alkylation under Mitsunobu conditions using bis-1,3-trityloxy-2-propanol as the alkylating agent. The bromo derivative **3.25** was heated at reflux with an excess of sodium iodide in dry acetone to give **3.26** in 95% yield. As expected, an upfield shift of the CH₂X was observed in the ¹H NMR spectrum, from δ 3.64 ppm in the starting material to δ 3.40 ppm in the desired product.

Synthesis of *N*3-benzoyl-*N*1-(3-bromopropyl)thymine and *N*3-benzoyl-*N*1-(3-iodopropyl)thymine

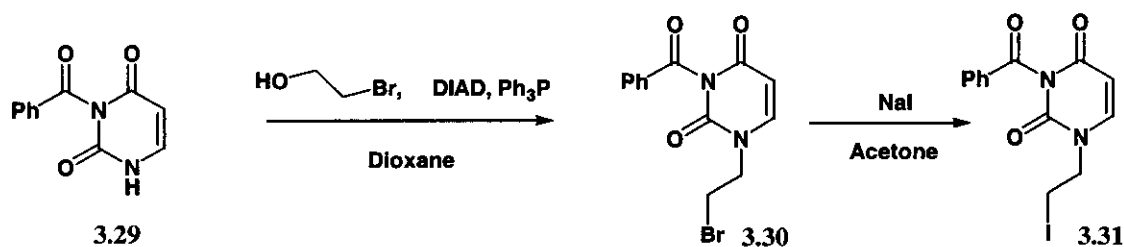
The Mitsunobu reaction was again carried out using **3.24** but substituting 3-bromopropan-1-ol for 2-bromoethanol (Scheme 3.15). The crude product was purified by column chromatography to give the desired *N*1 alkylated product **3.27** as a white solid in 92% yield. Compound **3.27** was then converted into its iodo derivative **3.28** by heating at reflux in the presence of an excess of sodium iodide in dry acetone overnight. In the ^1H NMR spectrum, the triplet signal corresponding to the CH_2Br at δ 3.91 ppm in the starting material was observed to shift upfield to δ 3.21 ppm. In the same way, the corresponding carbon signal in the ^{13}C NMR spectrum shifted from δ 29.34 ppm in the starting material to δ 1.62 ppm in the product.



Scheme 3.15

Synthesis of *N*3-benzoyluracil⁹³

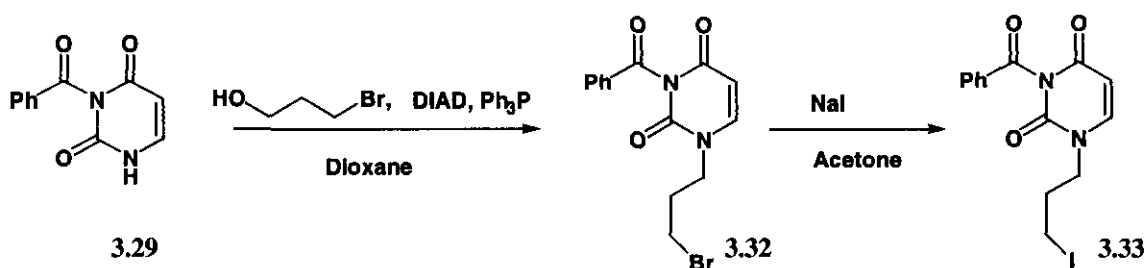
The same protecting group strategy as for thymine was also employed for uracil. Uracil was stirred with 2.2 equiv. of benzoyl chloride in acetonitrile-pyridine (5/2, v/v) at room temperature overnight (Scheme 3.16). It was noted that the addition of benzoyl chloride was exothermic. Benzoyl chloride was therefore added at 0°C via syringe pump over 1 h. After evaporation of the solvent the crude diprotected product could either be purified by column chromatography on basic alumina or treated with potassium bicarbonate as for diprotected thymine. Serendipitously, we found that the purification by column chromatography on basic alumina led to the desired removal of the protecting group at



Scheme 3.17

Synthesis of N3-benzoyl-N1-(3-bromopropyl)uracil and N3-benzoyl-N1-(3-iodopropyl)uracil

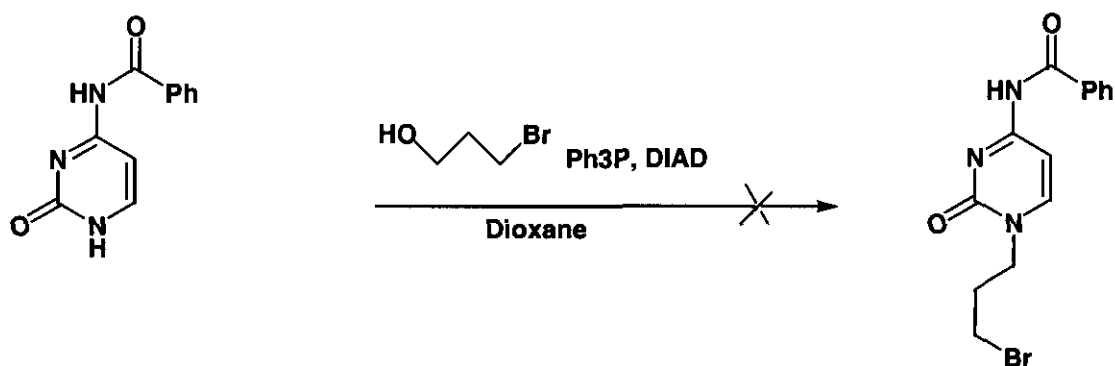
The Mitsunobu conditions were used to alkylate the *N*1 nitrogen of *N*3-benzoyluracil using 3-bromopropan-1-ol as the alkylating agent (Scheme 3.18). The reaction was carried out in the same way as for 2-bromoethanol. The desired bromo product **3.32** was isolated in 84% yield after purification by flash chromatography. Compound **3.32** was then converted into the iodo compound **3.33** by refluxing it with excess sodium iodide in dry acetone (96% yield from **3.32**). The upfield shift to δ 3.14 ppm of the triplet signal in the ¹H NMR spectrum for the CH₂X protons in the product compared with δ 3.44 ppm in the starting material confirmed that the reaction had indeed been successful.



Scheme 3.18

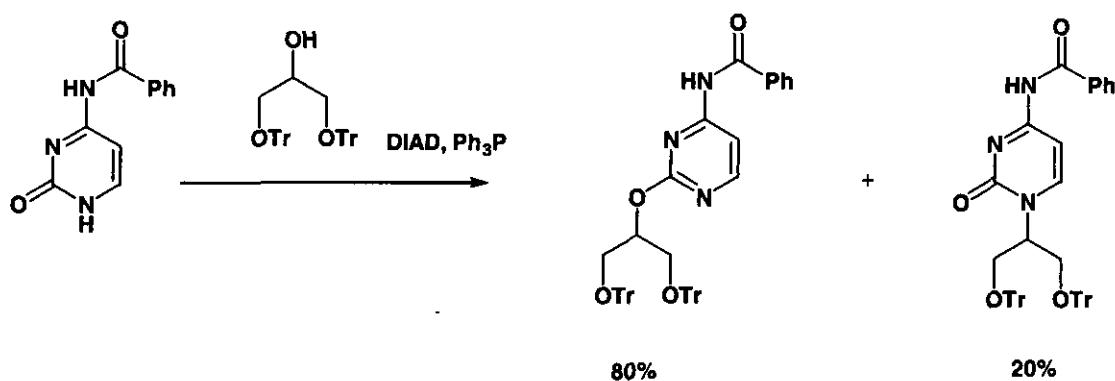
Synthesis of N4-benzoyl-N1-(3-bromopropyl)cytosine, and N4-benzoyl-N1-(3-iodopropyl)cytosine

A search for a protecting group for the *N4* exocyclic amino group in cytosine revealed that *N4*-benzoylcytosine was commercially available. It was therefore decided to try the usual Mitsunobu conditions on *N4*-benzoylcytosine (Scheme 3.19).



Scheme 3.19

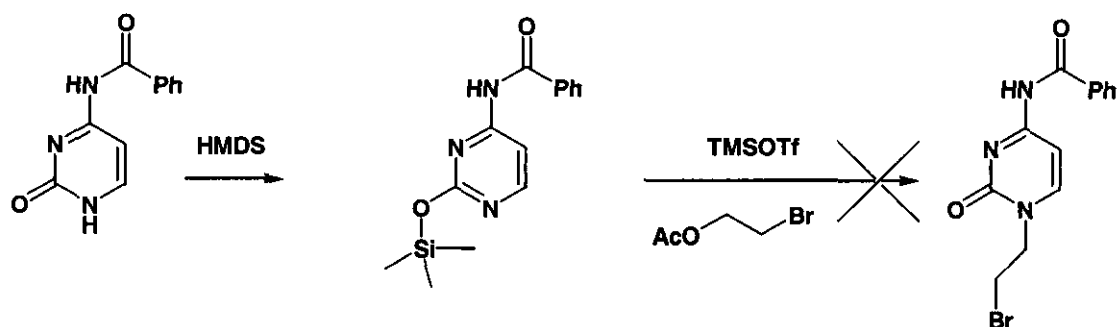
An NMR analysis of the reaction mixture revealed a very complex mixture of products and the absence of the desired product. It was later found in the literature that *N4*-benzoylcytosine undergoes alkylation on the oxygen of the ring carbonyl group. Thus, Lucas⁹² has observed that, regardless of the temperature (0°C , -78°C) or steric constraints (bulky alcohol or not), *O2*-alkylation was preferred. Scheiner has also obtained predominantly *O2*-alkylated products⁹⁴ (Scheme 3.20).



Scheme 3.20

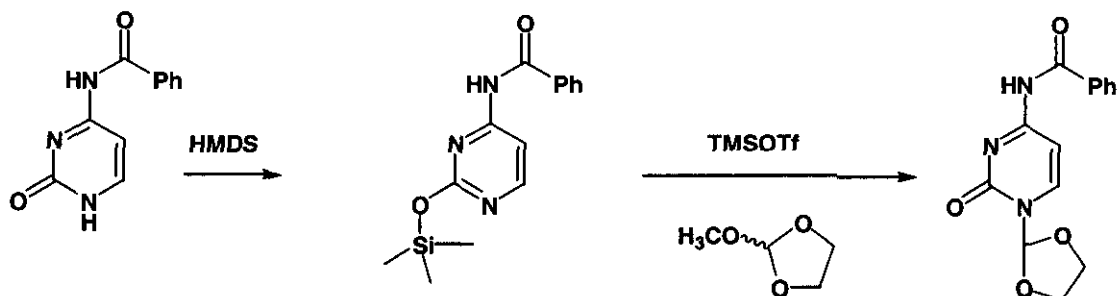
With these examples, it became clear to us that Mitsunobu-type conditions could not be used to alkylate cytosine. Consequently, we decided to attempt other literature methods to

access the desired *N*1 haloalkylated cytosine. One well known method for alkylation of cytosine is to use a silyl group to both protect the cytosine carbonyl group and direct the attack at the electrophilic centre adjacent to the acetate (Scheme 3.21).



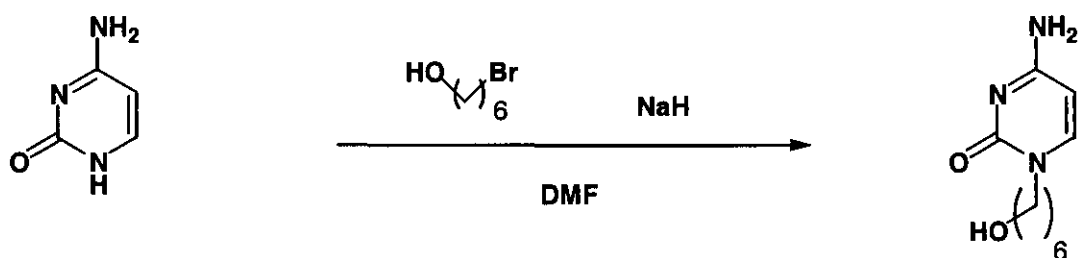
Scheme 3.21

Despite several attempts, this method was not successful in our case. Chu⁹⁵ has alkylated cytosine under similar conditions, but using a precursor containing a much more electrophilic centre due to the three neighbouring oxygen atoms (Scheme 3.22).



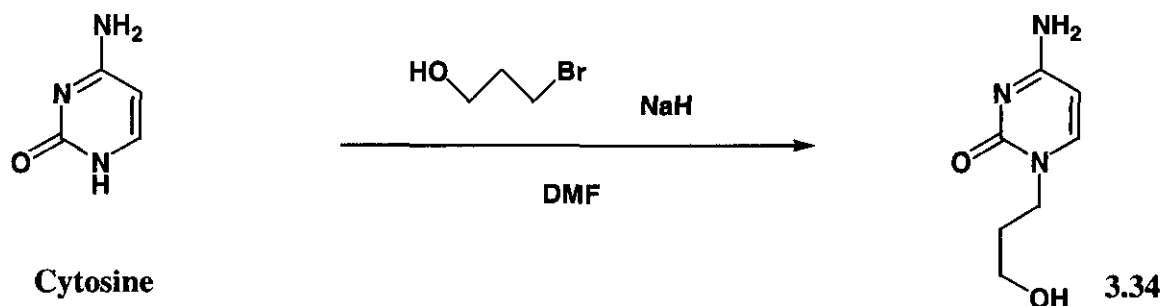
Scheme 3.22

In search for an alternative strategy, we found that Keese⁹⁶ had alkylated cytosine at the *N*1 position using 6-bromohexan-1-ol without the use of any protecting group for the exocyclic amine functionality (Scheme 3.23). Indeed, one advantage of this method is that there is no need for the removal of a protecting group.



Scheme 3.23

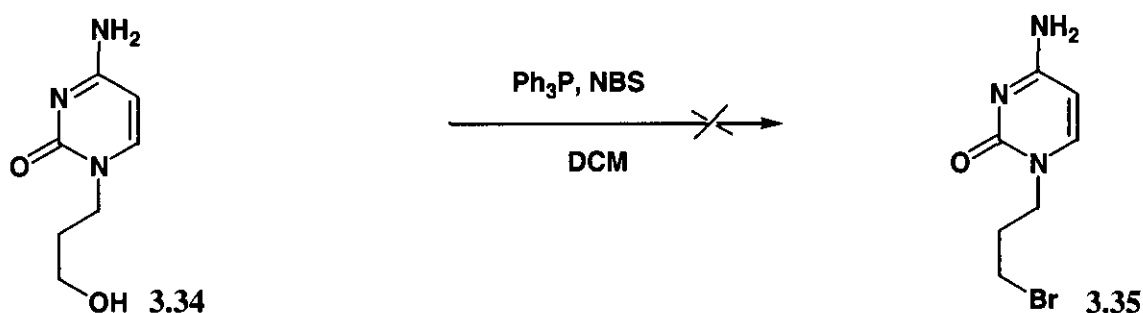
Further, we anticipated that the free amine would be compatible with the subsequent radical addition. Consequently, we adopted this method. Thus, NaH was added portionwise to cytosine in DMF (Scheme 3.24). After 1 h at room temperature, the solution became clear and 3-bromopropan-1-ol (0.5 equiv) was added dropwise to the solution. The mixture was stirred overnight at room temperature, quenched with methanol and the crude product was submitted to column chromatography. Due to the free amine group, triethylamine was required in order to elute the compound. The desired product **3.34** was isolated in 65% yield as a white solid. The presence of a singlet at δ 7.06 ppm integrating to two protons demonstrated that the free amine had not been alkylated. The chemical shift in the ¹H NMR spectrum of the triplet signal corresponding to the NCH₂ (δ 3.74 ppm) in our sample was very close to the triplet in Keese's product (δ 3.73 ppm⁹⁶). A triplet integrating to one proton at 3.44 ppm corresponded to the OH in the side chain. The accurate mass also gave satisfactory results (274.1194 for C₁₄H₁₅N₃O₃).



Scheme 3.24

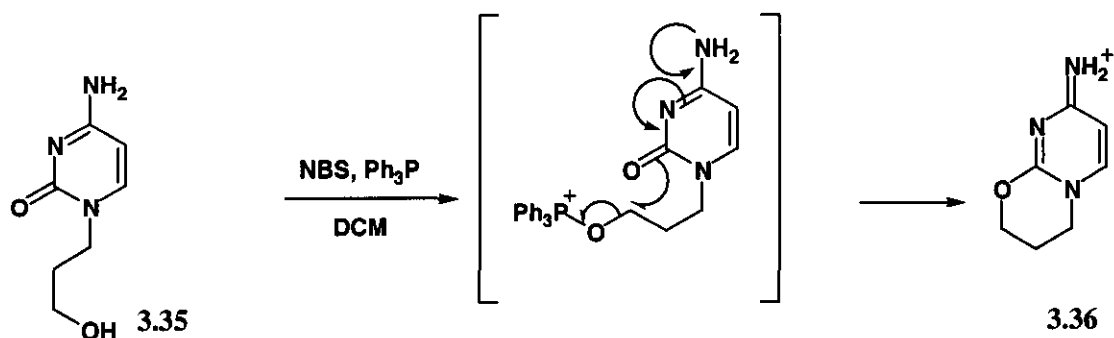
We then needed to convert the alcohol into the corresponding bromo compound. An obvious reagent for this is phosphorus tribromide. This reaction was carried out by dropwise addition of phosphorus tribromide to a stirred solution of the alcohol in

dichloromethane at -10°C . Monitoring the reaction by HPLC revealed the presence of numerous products, none of which could be isolated pure. It was then decided to use milder brominating conditions. We therefore selected the NBS/triphenylphosphine system. NBS was slowly added portionwise to a stirred solution of triphenylphosphine and alcohol **3.34** in dichloromethane (Scheme 3.25). The reaction mixture was stirred overnight after which time tlc showed no traces of starting material.



Scheme 3.25

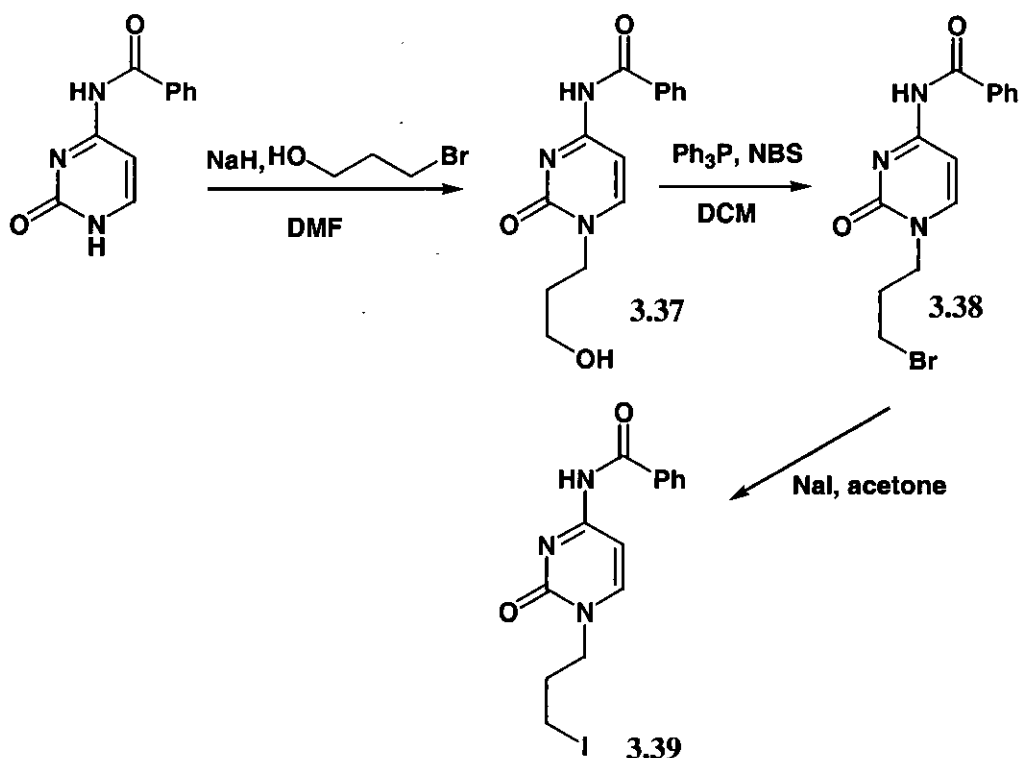
The crude product was purified by column chromatography using 10 % solution of acetic acid in methanol, but unfortunately the product isolated was the cyclised compound **3.36**. We observed a disappearance of the OH and NH_2 singlets at 4.61 and 7.06 ppm respectively in the product **3.36**. Presumably the presence of the lone pair of electrons on the exocyclic nitrogen promotes cyclisation (Scheme 3.26).



Scheme 3.26

It appeared, then, that the use of a protecting group on the amino group would be necessary so we decided to repeat these reactions using *N*4-benzoylcytosine (Scheme 3.27). Alkylation afforded a crude product that was purified by column chromatography on silica

gel to give the desired *N*1 alkylated cytosine **3.37** which gave satisfactory spectroscopic analysis.



Scheme 3.27

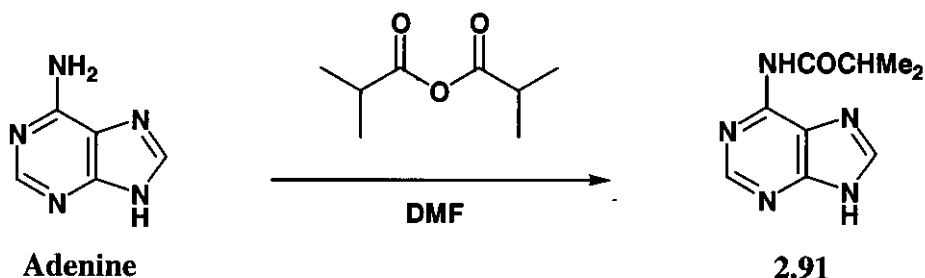
Conversion of the OH group to Br was carried out using NBS/triphenylphosphine in dichloromethane, and after purification by flash chromatography the desired product **3.38** was isolated in 72% yield (Scheme 3.27). The disappearance of the OH triplet at δ 4.65 ppm and of the CH_2OH quartet at δ 3.47 ppm in the ^1H NMR spectrum and the appearance of triplet at δ 3.50 ppm confirmed that the required conversion had indeed been accomplished.

The final step in the synthesis of our precursor for radical addition was the conversion of the bromopropyl cytosine derivative **3.38** into the iodo compound **3.39**. Again, this was easily achieved in the usual manner by heating the bromo compound **3.38** with an excess of sodium iodide at reflux in dry acetone. We noticed the usual upfield shift in the ^1H NMR spectrum of the triplet corresponding to the CH_2X from δ 3.47 ppm in **3.38** to δ 3.25 ppm in **3.39**. In the ^{13}C NMR spectrum the signal shifted from δ 31 ppm in the starting material to δ 19.03 in the product, in agreement with all the other iodo precursors.

3.2.2.2 Synthesis of haloalkylpurines

Synthesis of N6-(2-methylpropanoyl)adenine

As described in Chapter 2, Shevlin has used the 2-(methyl)propanoyl group as a protecting group for adenosine analogues⁷⁷.



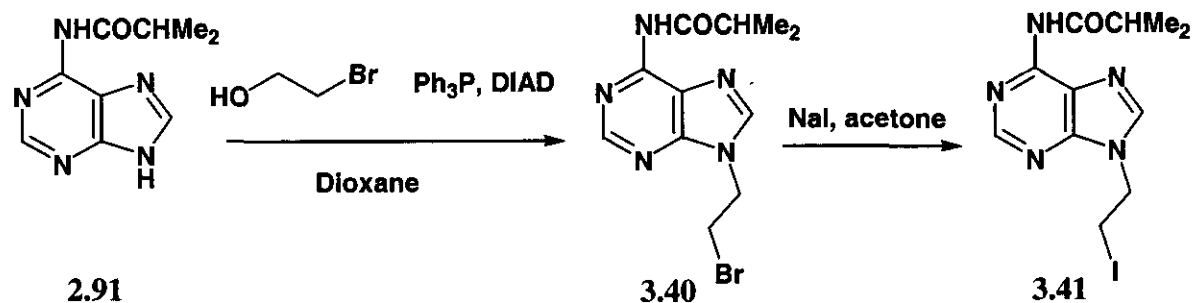
Scheme 3.28

We therefore chose to employ the same protection and prepared the corresponding *N*6-(2-methylpropanoyl)adenine **2.91** (Scheme 3.28). 6-Aminopurine (adenine) was stirred at reflux in DMF for 6 h with a three fold excess of 2-methylpropanoyl anhydride. The solution turned dark orange. After removal of the DMF under reduced pressure the yellow solid residue was refluxed in EtOH/H₂O (1/1). The reaction was stopped when the tlc showed that all diprotected (*N*6 and *N*9) adenine had been converted into the mono-protected compound **2.91**. The solvent was then evaporated and the yellow crude product dried over P₂O₅. The resulting solid which contained a substantial amount of adenine was further purified by column chromatography (DCM/MeOH, 9/1). This reaction could be performed on a large scale (up to 10 g adenine) without decrease in the yield (typically 70%).

As we had observed for *N*3-benzoyluracil, it was also found that the 2-methylpropanoyl group at position *N*9 could also be removed during column chromatography on basic alumina.

Synthesis of N9-(2-bromoethyl)-N6-(2-methylpropanoyl)adenine and N9-(2-iodoethyl)-N6-(2-methylpropanoyl)adenine

As Shevlin⁷⁷ had used Mitsunobu conditions to alkylate the N9 position of N6-(2-methylpropanoyl)adenine with 2-chloroethanol, we adopted an identical procedure using 2-bromoethanol (Scheme 3.29).

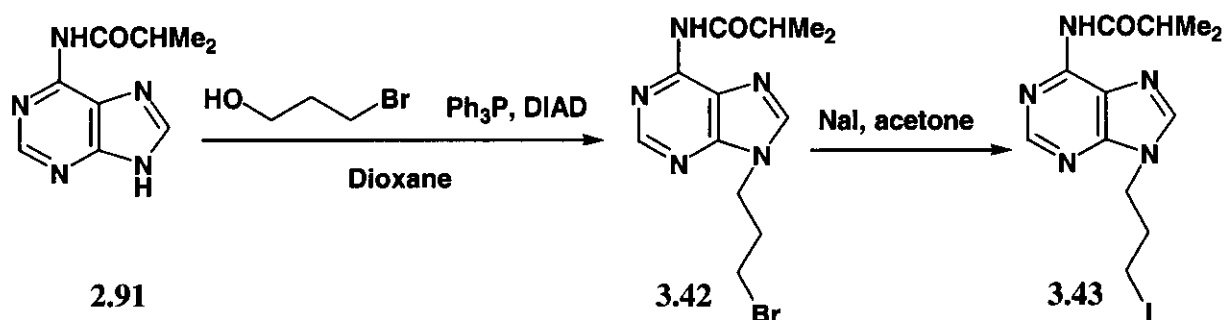


Scheme 3.29

Again, it was noted that when the addition of DIAD to compound **2.91** was performed at room temperature over 5 min, the reaction was exothermic and the yield of the alkylated product **3.40** was also lowered (typically <50%). Care had to be taken with the purification by column chromatography as the desired product **3.40** eluted very close to triphenylphosphine. To remove any residual traces of phosphine oxide the product was further purified by crystallisation from ethanol to yield 76% of **3.40**. The spectroscopic data of this bromo derivative were very similar to those of the chloro derivative of Shevlin. The bromoalkylated base was easily converted into the iodo compound **3.41** (86% from **3.40**) by refluxing **3.40** with an excess of sodium iodide in dry acetone in the dark. In the ¹H NMR spectrum we observed a characteristic shift of the CH₂X protons (triplet) from δ 3.79 in **3.40** to δ 3.63 ppm in **3.41**. The accurate mass (360.0315 for C₁₁H₁₄IN₅O) also confirmed that we have indeed incorporated an iodine atom into the molecule.

Synthesis of N9-(3-bromopropyl)-N6-(2-methylpropanoyl)adenine and N9-(3-iodopropyl)-N6-(2-methylpropanoyl)adenine

The Mitsunobu reaction was carried out between **2.91** and 3-bromopropan-1-ol (Scheme 3.30) to yield **3.42** (76%). Traces of triphenylphosphine oxide could be removed entirely by crystallisation from toluene. As previously described, the corresponding iodo derivative **3.43** was obtained in 81% yield by heating the bromo-derivative **3.42** at reflux overnight with excess sodium iodide in dry acetone. In the ^1H NMR spectrum, a shift in the signal for the CH_2X protons was observed from δ 3.37 ppm in the starting material to δ 3.12 ppm in the product. In the ^{13}C NMR spectrum, the signal for the carbon of the CH_2X system moved from δ 31.70 ppm in the starting material to δ 1.65 ppm in the product. The accurate mass also confirmed the structure of compound **3.43**.



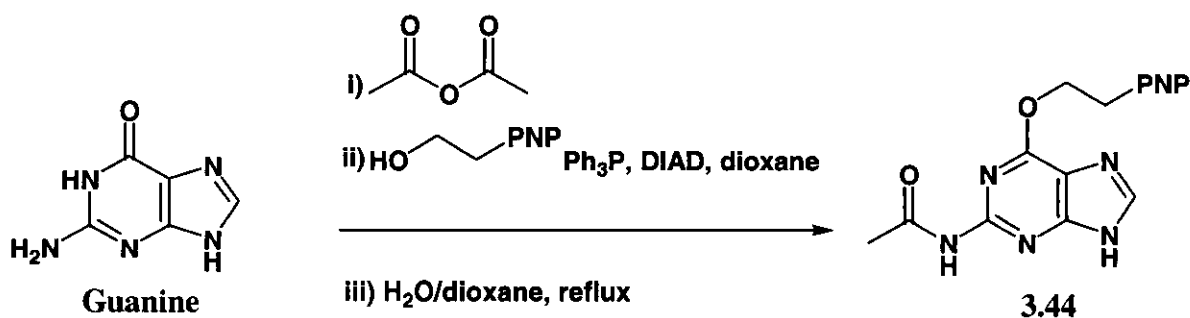
Scheme 3.30

Synthesis of N2-acetyl-O6-[2-(4-nitrophenyl)ethyl]guanine

While the reaction of adenine with ethylene carbonate in refluxing DMF is reported to give the desired N9-(2-hydroxyethyl)adenine in good yield, hydroxyethylation of guanine generates predominantly 7-substituted guanine⁹⁷. A literature search revealed that one of the commonly used approaches to 9-substituted guanine derivatives relies on the construction of the purine base step by step starting from 2-amino-4,6-

dichloropyrimidine⁹⁸. It was obvious that this reaction involved too many steps. In 1992, Benner and co-workers reported a convenient building block for the synthesis of analogues of guanosine⁹⁹. In their work, *N*2-(2-methylpropanoyl)-*O*6-[(4-nitrophenyl)ethyl]guanine **3.44** was used in the Mitsunobu reaction with sugars to produce exclusively *N*9-substituted guanosines.

Shevlin, in trying to make the above precursor, noted that treatment of *N*2-(2-methylpropanoyl)guanine with acetic anhydride repeatedly generated a mixture of *N*9-acetyl-*N*2-(2-methylpropanoyl)guanine together with *N*9,*N*2-diacetyl guanine¹⁰⁰. He therefore decided to use *N*9,*N*2-diacetyl guanine instead of *N*9-acetyl-*N*2-(2-methylpropanoyl)guanine. *N*9,*N*2-Diacetylguanine was readily prepared from guanine in one step by treatment with a large excess of acetic anhydride in refluxing DMF. Reaction of *N*9,*N*2-diacetyl guanine with 2-(4-nitrophenyl)ethanol and subsequent hydrolysis in refluxing dioxane-water gave *N*2-acetyl-*O*6-[2-(4-nitrophenyl)ethyl]guanine **3.44**.



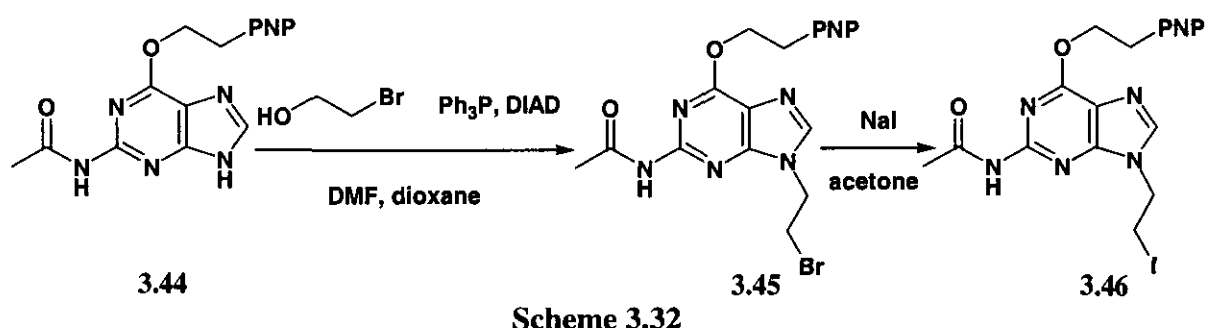
Scheme 3.31

In our hands, the diacetylated guanine produced under the same conditions as Shevlin was not purified but used directly in the next Mitsunobu step (Scheme 3.31). Thus, the unpurified diacetylated guanine was reacted with 2-(4-nitrophenyl)ethanol, triphenylphosphine and DIAD at room temperature overnight followed by reflux in dioxane/water (1/1) for 1 h. Upon cooling, the yellow precipitate was filtered and washed

several times with dichloromethane to remove triphenylphosphine oxide and any excess reagents. A pure sample of **3.44** was obtained in 53% yield by column chromatography on silica gel. The ^1H NMR spectrum of a repeat reaction showed that the crude product was pure enough (traces of phosphine oxide) to use it directly in the next step.

Synthesis of N2-acetyl-N9-(2-bromoethyl)-O6-[2-(4-nitrophenyl)ethyl]guanine and N2-acetyl-N9-(2-iodoethyl)-O6-[2-(4-nitrophenyl)ethyl]guanine

Mitsunobu reaction of **3.44** with 2-bromoethanol in the usual way (Scheme 3.32) afforded **3.45** in 67% yield after purification by column chromatography. With the aid of a ^1H - ^1H COSY experiment the assignment of the four triplet CH_2 signals [δ 3.28 ppm (ArCH_2), δ 3.95 and 4.55 ppm ($\text{NCH}_2\text{CH}_2\text{Br}$), δ 4.77 ppm (OCH_2)] could be achieved without ambiguity.



The bromo derivative **3.45** was then converted into the iodo compound **3.46** in 85% yield using the standard method. The CH_2X triplet in the ^1H NMR spectrum again shifted from δ 3.95 for **3.45** to δ 3.70 ppm in the product **3.46** which confirms the substitution. Moreover, the chemical shift in the ^{13}C NMR revealed CH_2X signal moved from δ 31.02 ppm in **3.45** to δ 3.65 ppm in **3.46** and the correct accurate mass (397.0412 for $\text{C}_{17}\text{H}_{17}\text{IN}_6\text{O}_4$) indicated that we had synthesised the desired iodoethyl guanine derivative **3.46** (Scheme 3.32).

3.2.2.3 Summary

We have shown that all five DNA bases could be alkylated regioselectively at the *N1* position for pyrimidines (thymine, uracil and cytosine) and at the *N9* position for purines (adenine and guanine). We were able to introduce both two- and three-carbon spacers between the nucleobase and the carbon atom that will become the radical centre. With these radical precursors to hand, we needed both to generate the carbon-centred radical by homolysis of the weak carbon-iodine bond and to form, stereoselectively, a carbon-carbon bond by addition of the radical to the dehydroalanine equivalent. These results are developed in the next section.

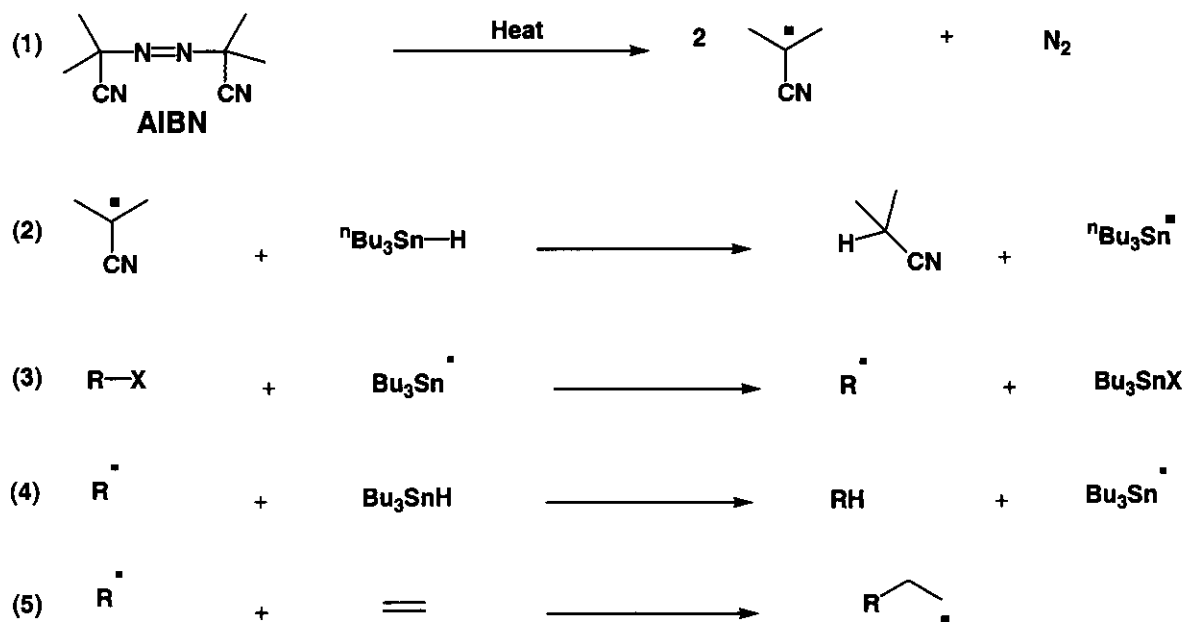
3.2.3 Radical addition

Oxazolidine-5-ones (e.g. **3.14**) have shown very good diastereoselectivity upon addition of a carbon-centered radical to the exocyclic double bond⁸⁸. We decided to use the *Z*-group to protect the ring nitrogen atom because it can be easily removed by hydrogenolysis in high yield.

There are several methods available to generate the required carbon-centred radicals. Amongst the most important are the tributyltin hydride, the catalytic tin hydride, and the mercury methods¹⁰¹. In our work only the former two methods of radical generation have been examined. The following is a short overview on C-C bond forming reactions that employ such tin-based methods.

Radical reactions are usually chain processes, and a chain-carrier radical is required. This is very commonly a trialkyltin radical. The generation of such radicals is commonly achieved using the initiation sequence shown in Scheme 3.33. Here, the formation of radicals is brought about by the thermolysis of azobis-(isobutyronitrile) (AIBN) (step 1). The correct choice of initiator is usually decided by the operating temperature and hence

by the appropriate half-life of the decomposition reaction; AIBN has a half-life of 2 h at 80°C or 0.1 h at 100°C.

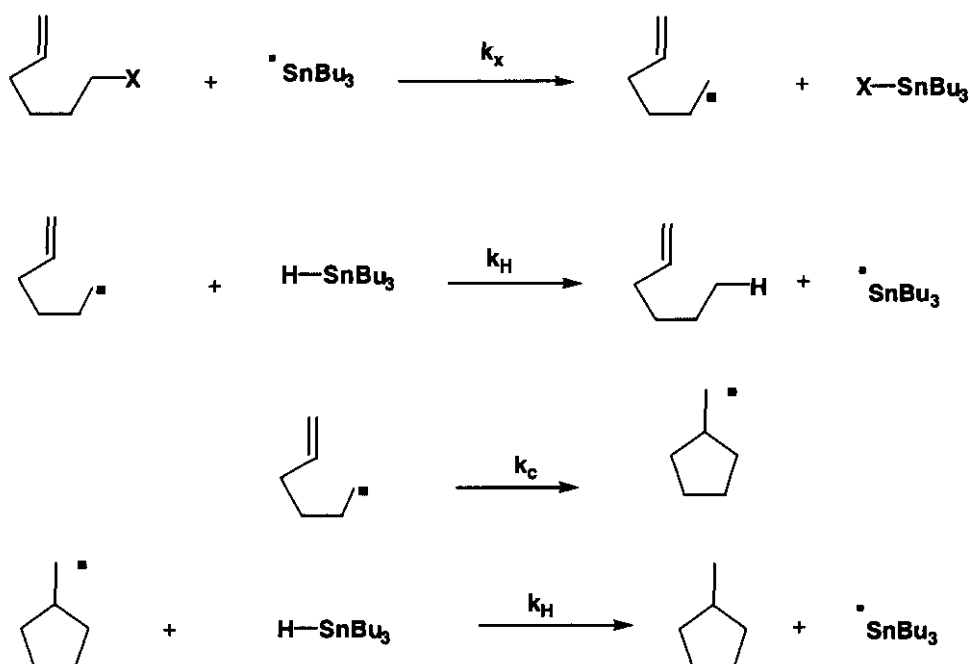


Scheme 3.33

The AIBN-derived radical then abstracts a hydrogen atom from a tin hydride to form a tin-centered radical (step 2). This trialkyltin radical generated by the initiator can abstract a halogen atom from the haloalkane, thereby producing the desired carbon-centered alkyl radical (step 3). The carbon-centered radical can then be reduced by hydrogen abstraction from another tin hydride molecule (step 4) or alternatively it could add to an alkene to extend the radical structure (step 5). The choice of the halogen in the haloalkane is important because the C-X bond dissociation energies (BDEs) are different: for C-Cl, C-Br and C-I the BDEs are, respectively, 340, 290 and 220 kJmol⁻¹. Thus iodoalkanes require little initiation. A trace of oxygen is sufficient to generate a tin-centered radical from the trialkyltin hydride by homolytic cleavage of the tin-hydrogen bond. Thereafter, almost every encounter between the trialkyltin radical and the iodoalkane is productive.

A classic example of a synthetically useful process is the tributyltin hydride mediated cyclisation of the 5-hexenyl radical to form methylcyclopentane (Scheme 3.34). The Bu₃Sn• radical abstracts the halogen atom to provide the 1-hexen-6-yl radical. In a second-

order reaction, this radical can abstract a hydrogen atom from the tin hydride reagent to afford the reduced product, 1-hexene, with concomitant regeneration of a tributyltin radical. Alternatively, the hexenyl radical can undergo a first order irreversible 5-*exo-trig* ring closure to form the cyclopentylmethyl radical. This latter radical can itself abstract a hydrogen atom from the tin hydride reagent to afford methylcyclopentane. Thus, the relative amounts of 1-hexene and methylcyclopentane are determined by the relative rates for the partitioning of the 1-hexen-6-yl radical between cyclisation (k_c) and hydrogen atom abstraction ($k_H[\text{Bu}_3\text{SnH}]$). Thus, the tin hydride concentration provides a variable by which the product distribution can be controlled. At a very high concentration ($> 5 \text{ M}$), the unrearranged hex-1-ene product will predominate, whereas at low concentration ($< 0.05 \text{ M}$), the major product will be methylcyclopentane.



Scheme 3.34

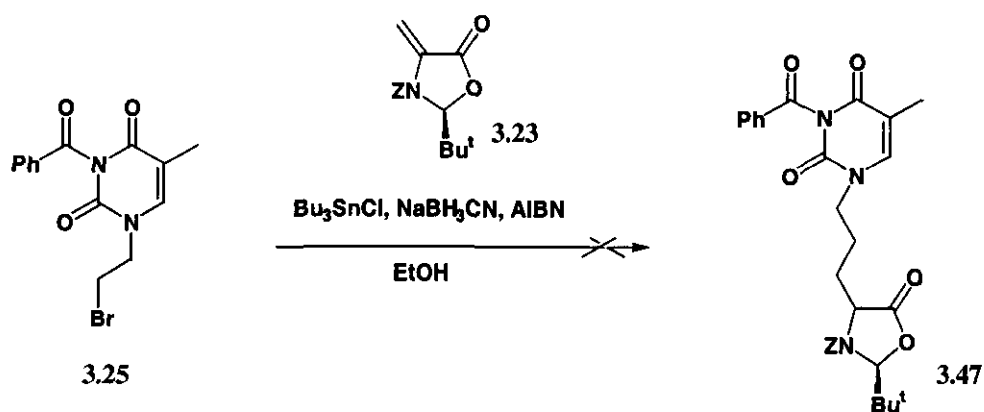
Of course, these observations are also true for intermolecular addition of a carbon-centred radical to an alkene. By adjustment of the tin hydride concentration, a window of radical lifetime is obtained that allows for the slower addition to alkenes. One common technique used to maintain a low tin hydride concentration is the use of slow addition *via* syringe pump; this bypasses the need for a large volume of solvent as diluent. Another technique is

the *in situ* generation of tin hydride; this enables low standing concentrations to be achieved. Whereas the tin hydride method requires stoichiometric amounts of tin reagent, the *in situ* generation of a tin hydride from the corresponding tin chloride is a catalytic procedure that was developed by Corey and Suggs¹⁰². In this procedure, as it is formed during the reaction, the tin chloride is reduced to the corresponding tin hydride using sodium borohydride or sodium cyanoborohydride. The tin hydride is then oxidised into the tin iodide (formed from the haloalkane) hence forming the desired carbon centred radical for radical addition. The so-formed tin iodide is further reduced to tin hydride and this completes the catalytic cycle.

Both the tributyltin hydride and the catalytic tributyltin chloride method have been used in the present work.

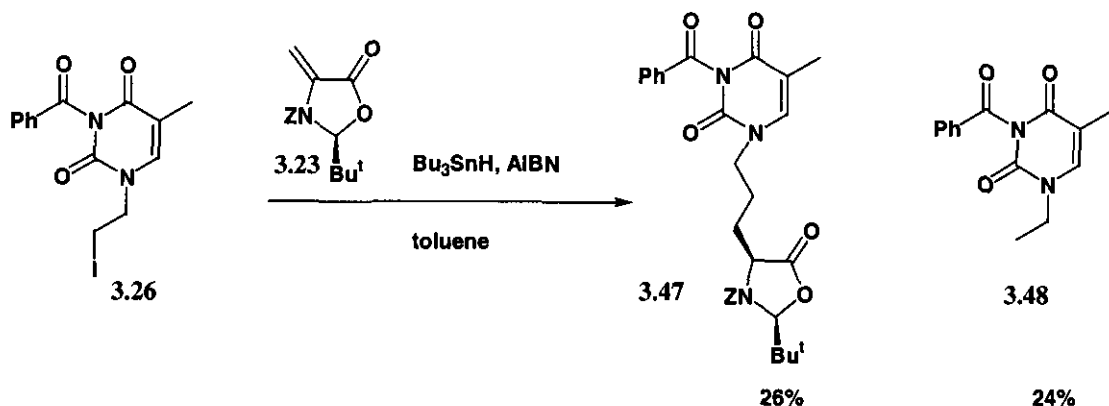
3.2.3.1 Thymine adducts

The preparation of the thymine bromo- and iodo-ethyl **3.25** and **3.27**, and -propyl derivatives **3.26** and **3.28** has been described above. The first reaction to be performed employed the bromoethyl derivative **3.25**. Using this, we tried to generate the corresponding radical *via* catalytic formation of tributyltin hydride from the reduction of tributyltin chloride (0.2-0.3 equiv.) by sodium cyanoborohydride (Scheme 3.35) in the presence of the oxazolidinone **3.23**. However, after 3h reflux in ethanol no addition product could be isolated. Indeed, the bromoethyl starting material was recovered in 82% yield.



Scheme 3.35

Consequently, we decided to repeat the reaction using the iodoethyl derivative **3.26**. We also decided to adopt the conventional tin hydride procedure (Scheme 3.36).

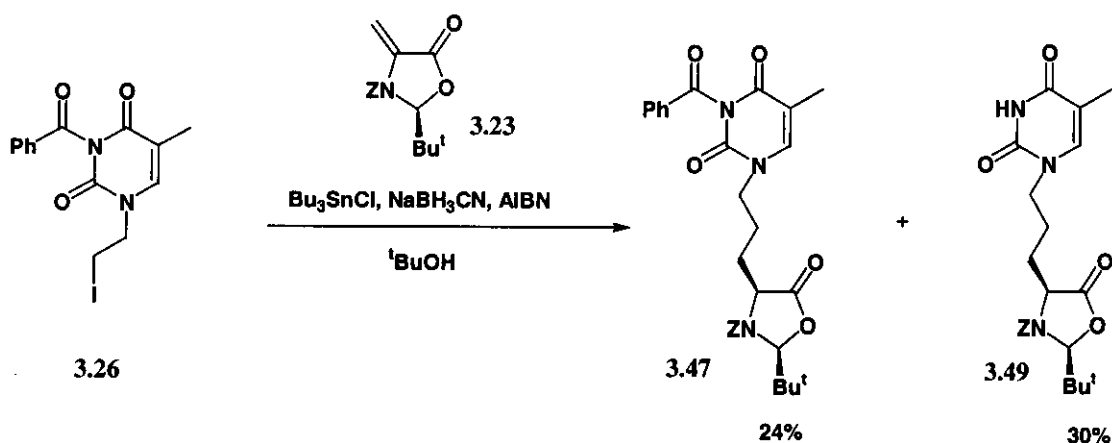


Scheme 3.36

Tributyltin hydride was added *via* syringe pump over 2 h to a refluxing solution of the iodoethyl compound **3.26**, chiral template **3.23** and AIBN in toluene. The concentration of **3.26** was calculated to be roughly 0.01M so as to minimise formation of the reduction product. Gratifyingly, the desired adduct **3.47** was isolated after column chromatography in 26% yield, although the reduction compound **3.48** was also isolated in 24% yield. The adducts were all 2,4-*syn* and this will be discussed later.

To reduce the amount of **3.48** produced still further, rather than use impractical volumes of solvent (so as to run the reaction at low concentration). We decided to employ the catalytic tributyltin chloride method (Scheme 3.37). Thus, the chiral template **3.23** (2 equiv.), the iodoethyl thymine derivative **3.26**, tributyltin chloride (0.2-0.3 equiv.), sodium cyanoborohydride (2 equiv.) and AIBN were stirred at reflux in *tert*-butanol for 16 h.

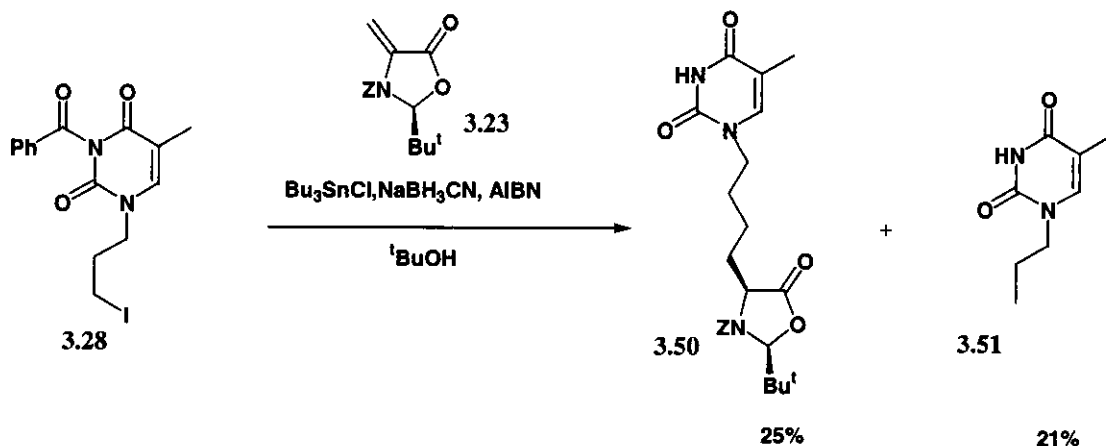
Work-up afforded 24% of the desired adduct **3.47** and also, unexpectedly, the 3-debenzoylated adduct **3.49**; no reduction product was isolated. It would appear that the catalytic tin hydride method does indeed lower the relative amount of the reduction product and, more importantly, more than doubled the yield of the desired adduct (from 26% to a combined yield of 54%).



Scheme 3.37

It was decided to investigate further the debenzoylation process. The reaction was repeated, but reflux was continued for 40 h instead of 16 h. This resulted in complete 3-debenzoylation, the yield of **3.49** being 47%.

We therefore attempted radical addition using the iodopropylthymine derivative **3.28** under identical conditions (Scheme 3.38).



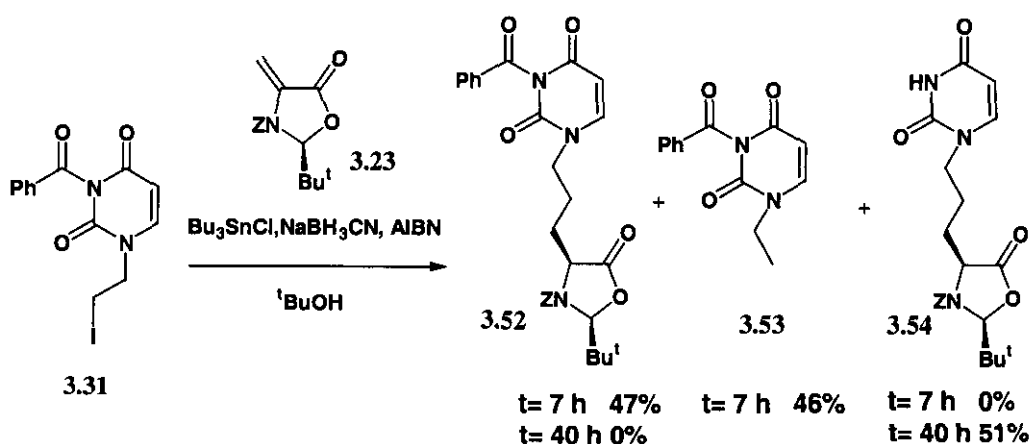
Scheme 3.38

As expected, upon reaction at reflux for 40 h in the presence of 2.0 equiv of sodium cyanoborohydride, the 3-debenzoylated adduct **3.50** was isolated after column chromatography in 25% yield, although the 3-debenzoylated reduction product, propylthymine **3.51** was also isolated in 21% yield.

Nevertheless, encouraged by these results, we decided to employ the radical addition using the uracil precursors.

3.2.3.2 Uracil adducts

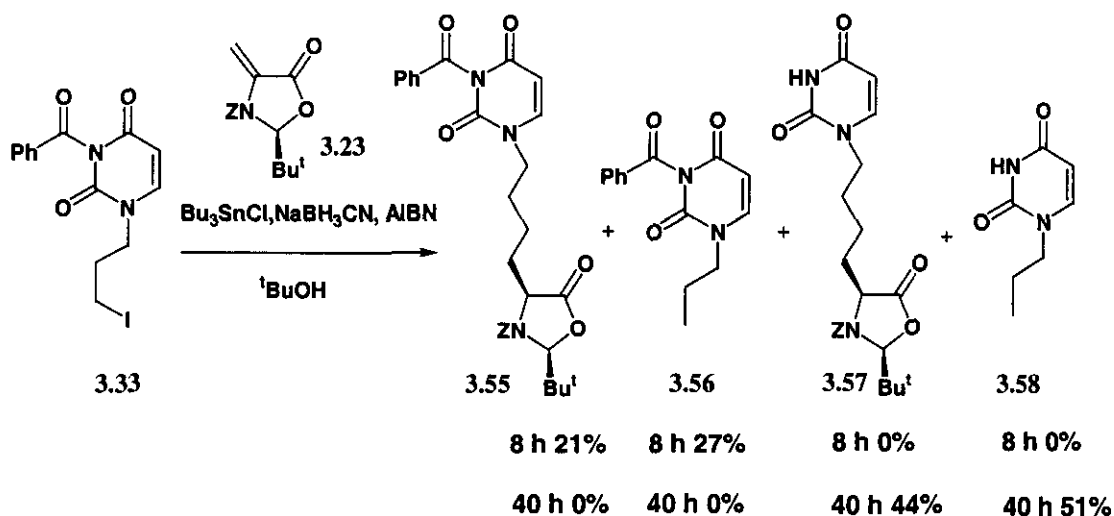
As the $\text{Bu}_3\text{SnCl}/\text{NaBH}_3\text{CN}$ (0.3/2 equiv.) method gave satisfactory results, this method was applied to the corresponding iodouracil precursors (Schemes 3.39 and 3.40).



Scheme 3.39

Thus, from the iodoethyl starting material **3.31**, the desired compound **3.52** was isolated in 47% yield after reflux for 7 h in *tert*-butanol. The benzoylated reduced compound **3.53** was also formed in 46% yield. A second reaction involving reflux for 40 h gave as by now expected the 3-debenzoylated adduct **3.54** in 51% yield.

A similar reaction involving the iodopropyluracil precursor at reflux for 8 h (Scheme 3.40) gave the desired adduct **3.55** in 21% yield and the reduction product **3.56** in 27% yield. Extended reaction time gave as expected the desired debenzoylated adduct **3.57** in 44% yield. 1-Propyluracil **3.58**, was also isolated as a reduction co-product in 51% yield.

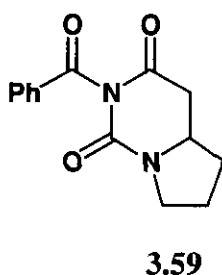


Scheme 3.40

In an attempt to improve the yield of the product **3.57** of conjugate addition, this reaction was repeated using an excess of chiral acceptor **3.23** (5.0 equiv.). The adduct **3.57** was isolated in 62% yield. Despite the improved yield, we concluded that the latter conditions were too wasteful of our valuable chiral oxazolidinone **3.23**.

3.2.3.3 An unexpected intramolecular radical addition

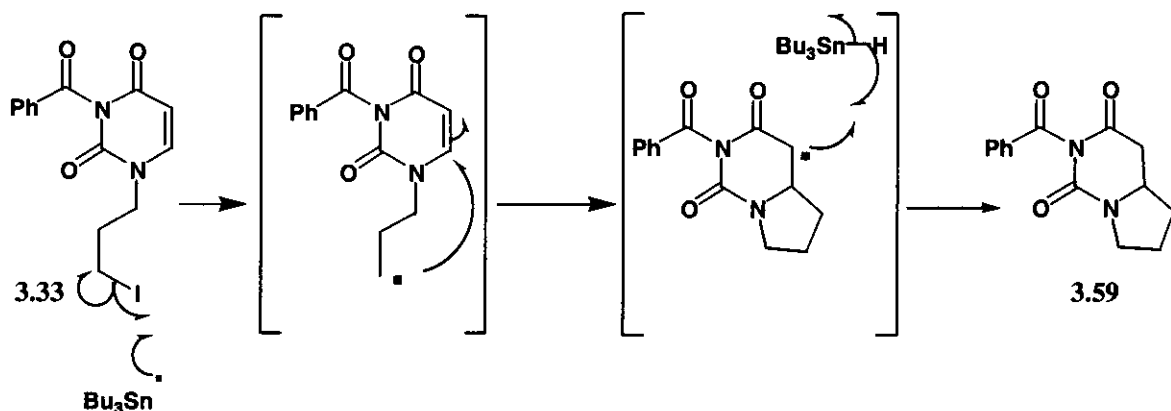
Given that the use of 2 mol equiv. of sodium cyanoborohydride resulted in both radical addition and deprotection of the nucleic acid base, we decided to investigate the reaction using 0.3 mol equiv, keeping the amount of Bu_3SnCl the same (3 equiv.).



The reaction mixture was refluxed for 30 min in *tert*-butanol, after which time 82% of the unreacted chiral template **3.23**, along with 80% of the starting iodopropyl compound **3.33** was recovered. Unexpectedly, we also isolated the bicyclic product **3.59** in 87% yield (based on recovered **3.33**). In other words, essentially all the radical species resulting from

the homolytic cleavage of the weak iodine-carbon bond underwent intramolecular addition rather than intermolecular capture by the radical template. According to Baldwin's rules, the cyclisation is a 5-*exo-trig* process and therefore favoured.

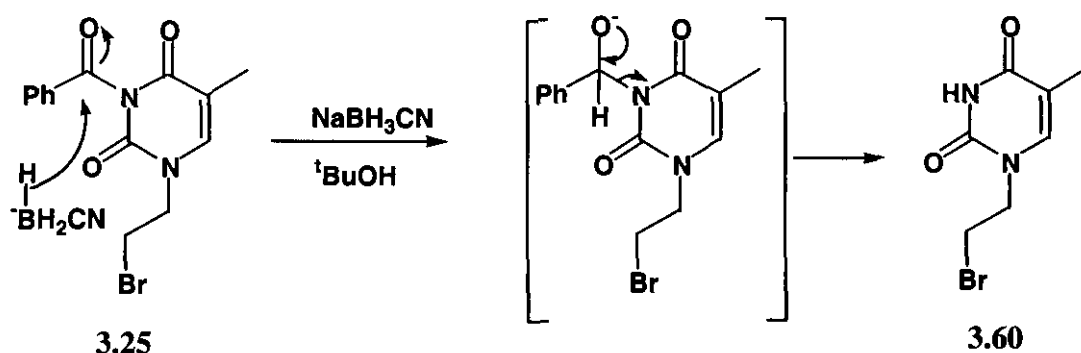
The reaction was repeated using tributyltin hydride and AIBN in the absence of any oxazolidinone **3.23**. The bicyclic compound **3.59** was the only product isolated (53% yield) from this reaction. The probable mechanism for the intramolecular addition is shown below (Scheme 3.41)¹⁰³.



Scheme 3.41

3.2.3.4 Sodium cyanoborohydride and deacylation

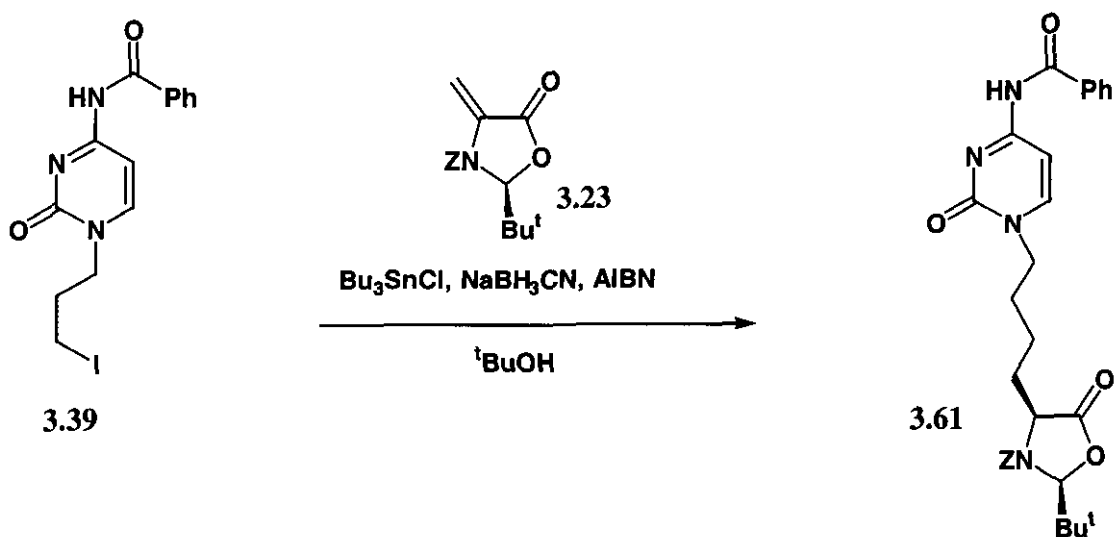
To determine whether or not the deacylation was a radical-initiated process, compound **3.25** was heated at reflux in *tert*-butanol with 1 equivalent of sodium cyanoborohydride. The debenzoylated product **3.60** was isolated, indicating that deacylation was more likely to be hydride-mediated, rather than a radical-mediated process (Scheme 3.42). It is believed that the benzoyl carbonyl group of compound **3.25** is out-of plane of the thymine ring and therefore is not really amide-like. This ketone-like carbonyl can therefore be reduced to the corresponding alcohol by sodium cyanoborohydride and can further collapse to give benzaldehyde and compound **3.60**.



Scheme 3.42

3.2.3.5 Cytosine adduct

The radical addition reaction was also performed on the iodopropyl cytosine **3.39** (Scheme 3.43). Unfortunately, the corresponding adduct **3.61** could not be separated from a mixture with, *inter alia*, the reduced cytosine starting material and unknown by-products. High resolution mass spectrometry verified the presence of **3.61** so the crude mixture containing the addition product was taken through to the next step (see section 3.2.4).

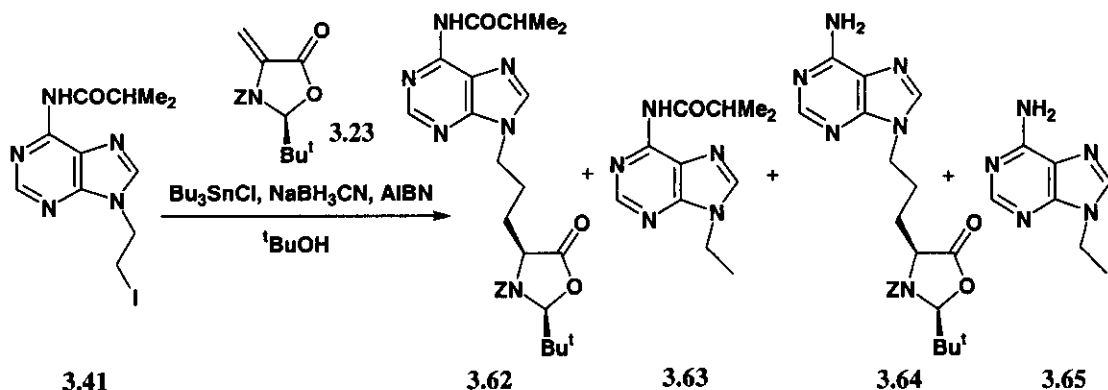


Scheme 3.43

3.2.3.6 Adenine adducts

In the purine series, the usual $\text{Bu}_3\text{SnCl}/\text{NaBH}_3\text{CN}$ method was applied to the iodoethyl adenine compound **3.41** (Scheme 3.44). After 16 h reaction time a mixture of products

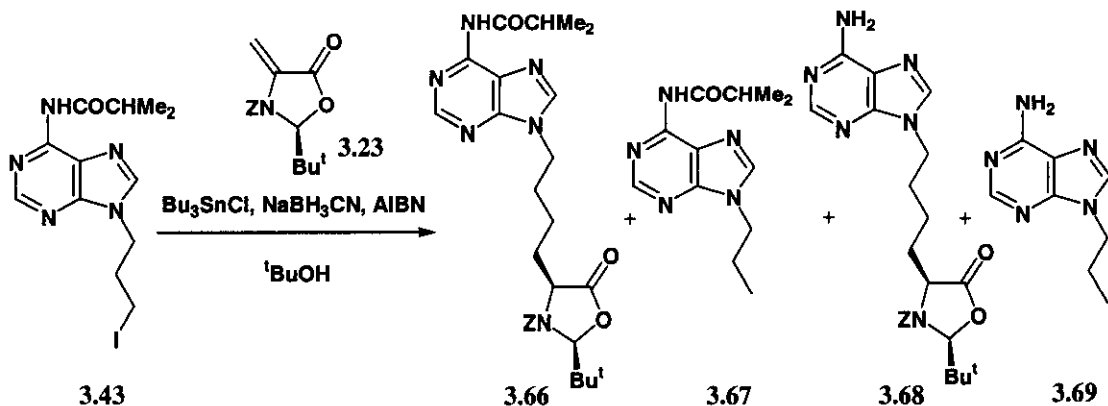
resulting from conjugate addition [40%; acylated **3.62** (26%) and deacylated **3.64** (14%)] and reduction [36%; acylated **3.63** (17%) and deacylated **3.65** (19%)] was obtained.



Scheme 3.44

The deacylated adduct **3.64** and acylated reduction product **3.63** were isolated as an inseparable mixture, the contents of which were quantified from the result of the subsequent hydrolysis step (see below). The compounds **3.62**, **3.63**, **3.64**, **3.65** showed satisfactory spectral data.

The iodopropyl derivative **3.43** similarly gave products of radical addition [22%; acylated **3.66** (12%) and deacylated **3.68** (10%)] along with reduced compounds [24%; acylated **3.67** (11%) and deacylated **3.69** (23%)] (Scheme 3.45).

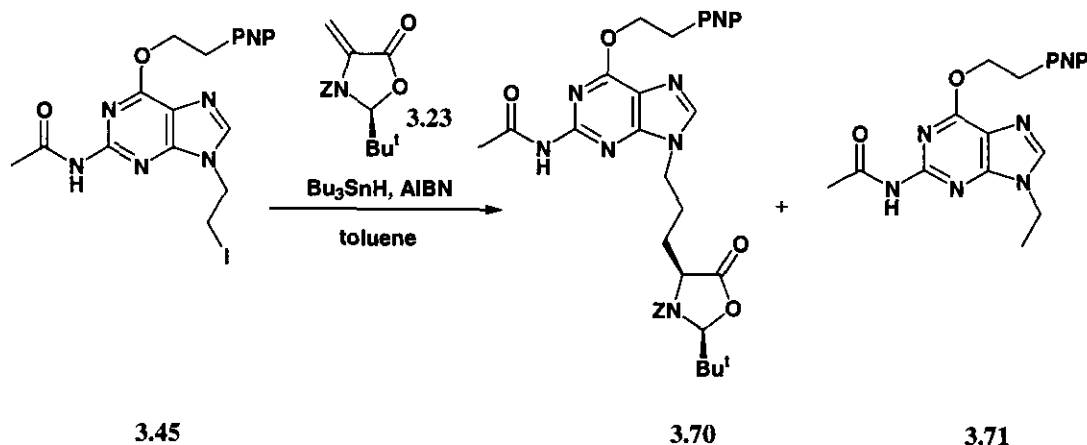


Scheme 3.45

For comparison, we found that the Bu_3SnH method when applied to iodopropyl compound **3.43** led to the acylated adduct **3.66** in 23% yield and the reduction product **3.67** in 45% yield.

3.2.3.7 Guanine adduct

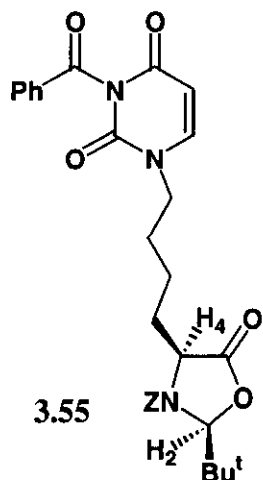
Finally, conjugate addition between the guanine derivative **3.45** and the methylenioxazolidinone **3.23** using the Bu_3SnH method led to adduct **3.70** (21%) and reduction product **3.71** (20%) (Scheme 3.46). This conjugate addition reaction was also conducted using the catalytic tin chloride method in *tert*-butanol. Unfortunately, no addition product was detected.



Scheme 3.46

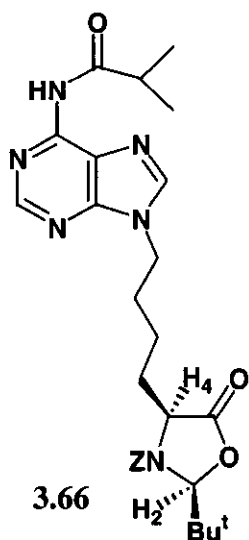
3.2.3.8 Diastereoselectivity of the radical addition

A major goal of our work was to carry out the synthesis of amino acids in a stereoselective manner. In the above radical additions, only one diastereoisomer was detected in the ^1H NMR spectra. To determine the relative stereochemistry of the radical addition (*syn* or *anti* addition) of the purinyl and pyrimidyl radicals onto the electron deficient alkene of the oxazolidinone **3.23**, we performed n.O.e. experiments on the radical adducts. The corresponding results for the three examples are presented in tables 3.4, 3.5 and 3.6.



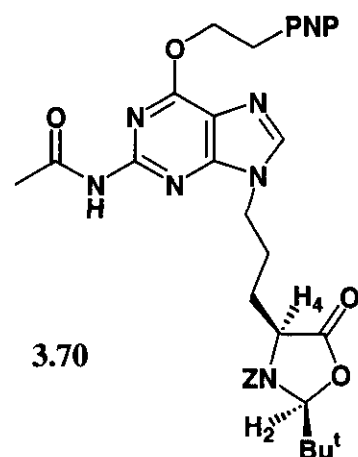
Signal irradiated	Signal enhanced
Bu ^t	H ₂ (2.61 %), CH ₂ CH ₂ CH ₂ N (0.24 %)
H ₂	H ₄ (1.26 %), Bu ^t (5.12 %)
H ₄	H ₂ (1.24 %)

Table 3.4



Signal irradiated	Signal enhanced
Bu ^t	H ₂ (1.92 %), CH ₂ CH ₂ CH ₂ N (0.82 %)
H ₂	H ₄ (0.94 %), Bu ^t (3.52 %)
H ₄	H ₂ (0.46 %)

Table 3.5

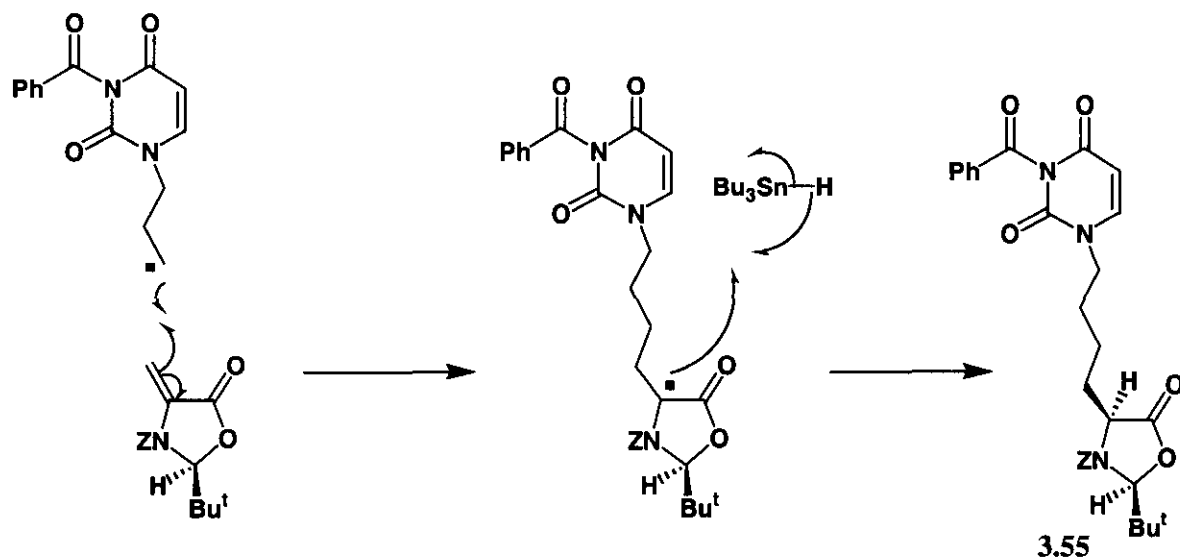


Signal irradiated	Signal enhanced
Bu ^t	H ₂ (2.6 %)
H ₂	H ₄ (1.12 %), Bu ^t (5.21 %)
H ₄	H ₂ (1.63 %)

Table 3.6

Since all of these n.O.e. experiments exhibited, *inter alia* mutual enhancement between C-2(H) and C-4(H), we concluded that the radical addition was *syn* to the C2 *tert*-butyl group. The rationale for this *syn* addition is outlined in Scheme 3.47. Addition of the alkyl

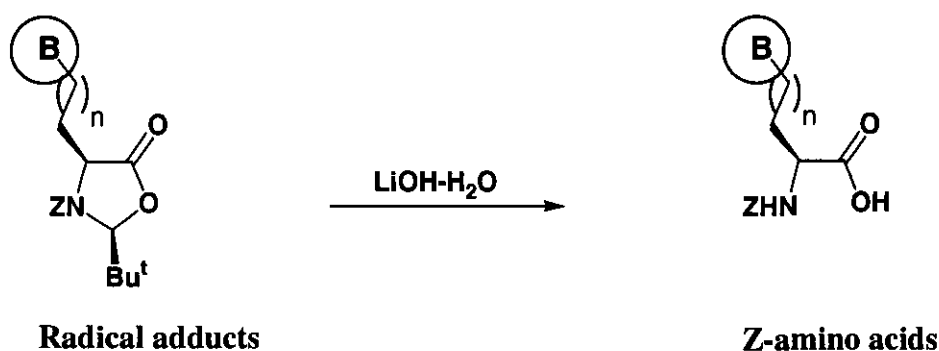
radical yields an aminoacyl radical intermediate that reacts with tributyltin hydride on the less hindered face of the oxazolidine.



Scheme 3.47

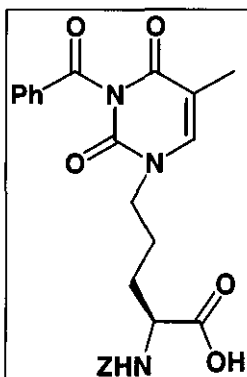
3.2.4 The Z-protected amino acids

The chiral template was removed from the adduct oxazolidinones by base hydrolysis using LiOH in THF/ H_2O at 0°C for 30 min (Scheme 3.48)¹⁰⁴.

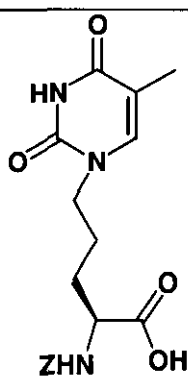


Scheme 3.48

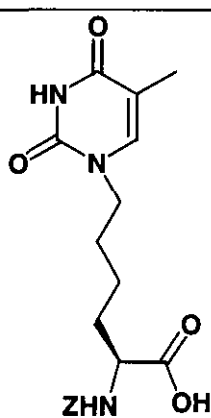
A simple acidification of the crude mixtures using aqueous HCl, followed by extraction of the acids using ethyl acetate afforded the desired Z-protected amino acids **3.73-3.83**. In the case of the guanine derivative **3.83** some solubility problems were encountered at the extraction stage, but these were overcome by using DCM. For the cytosine example **3.78**, the crude product **3.61** from radical addition was used in the hydrolysis, unfortunately no pure Z-amino acid **3.78** was obtained and **3.78** was used as crude in the next step. Thus, the Z-protected amino acids were afforded in high yield (Table 3.7).



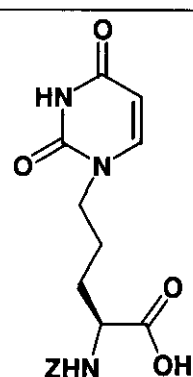
3.72



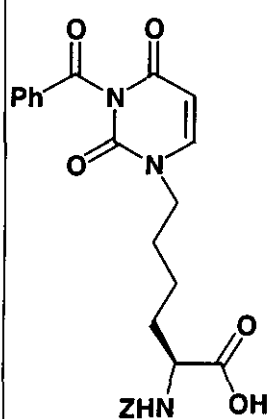
3.73



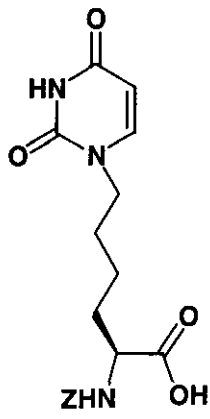
3.74



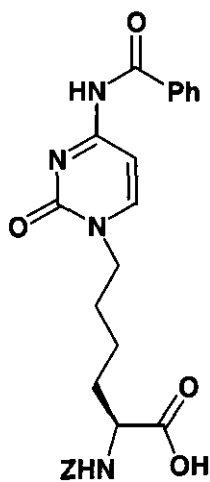
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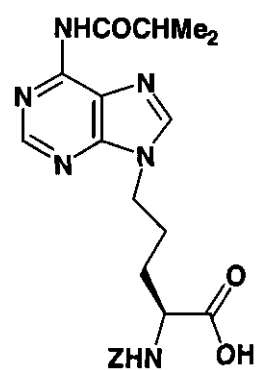
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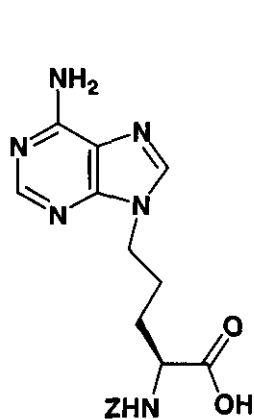
3.77



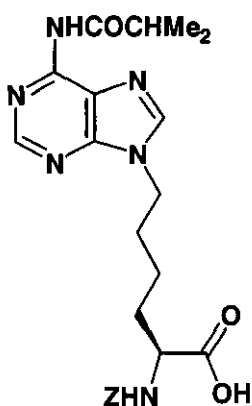
3.78



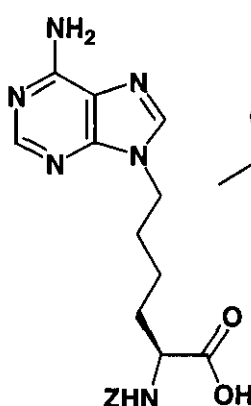
3.79



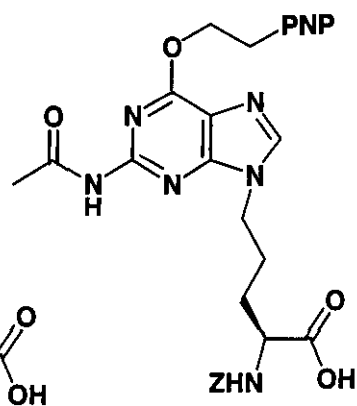
3.80



3.81



3.82



3.83

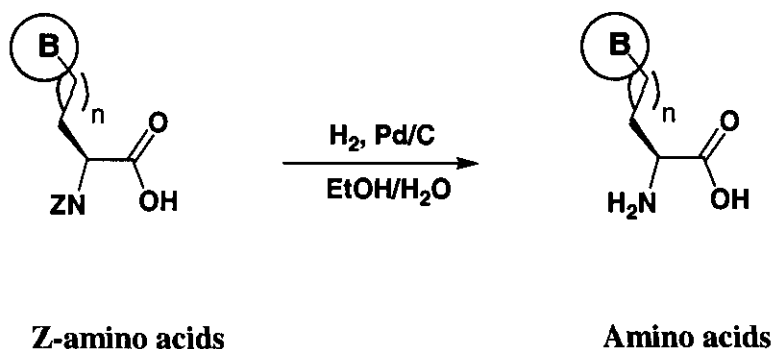
Oxazolidinone adduct	Z-amino acid	Yield (%)	Amino acids	Yield (%)
3.47	3.72	92	-	-
3.49	3.73	96	3.84	74
3.50	3.74	87	3.85	79
3.54	3.75	69	3.86	75
3.55	3.76	96	-	-
3.57	3.77	52	3.87, 3.88	90, 88
3.61	3.78	crude	3.89	-
3.62	3.79	72	3.90	75
3.64	3.80	87	-	-
3.66	3.81	89	3.91	61
3.68	3.82	86	-	-
3.70	3.83	87	-	-

- : reaction not carried out

Table 3.7

3.2.5 The amino acids

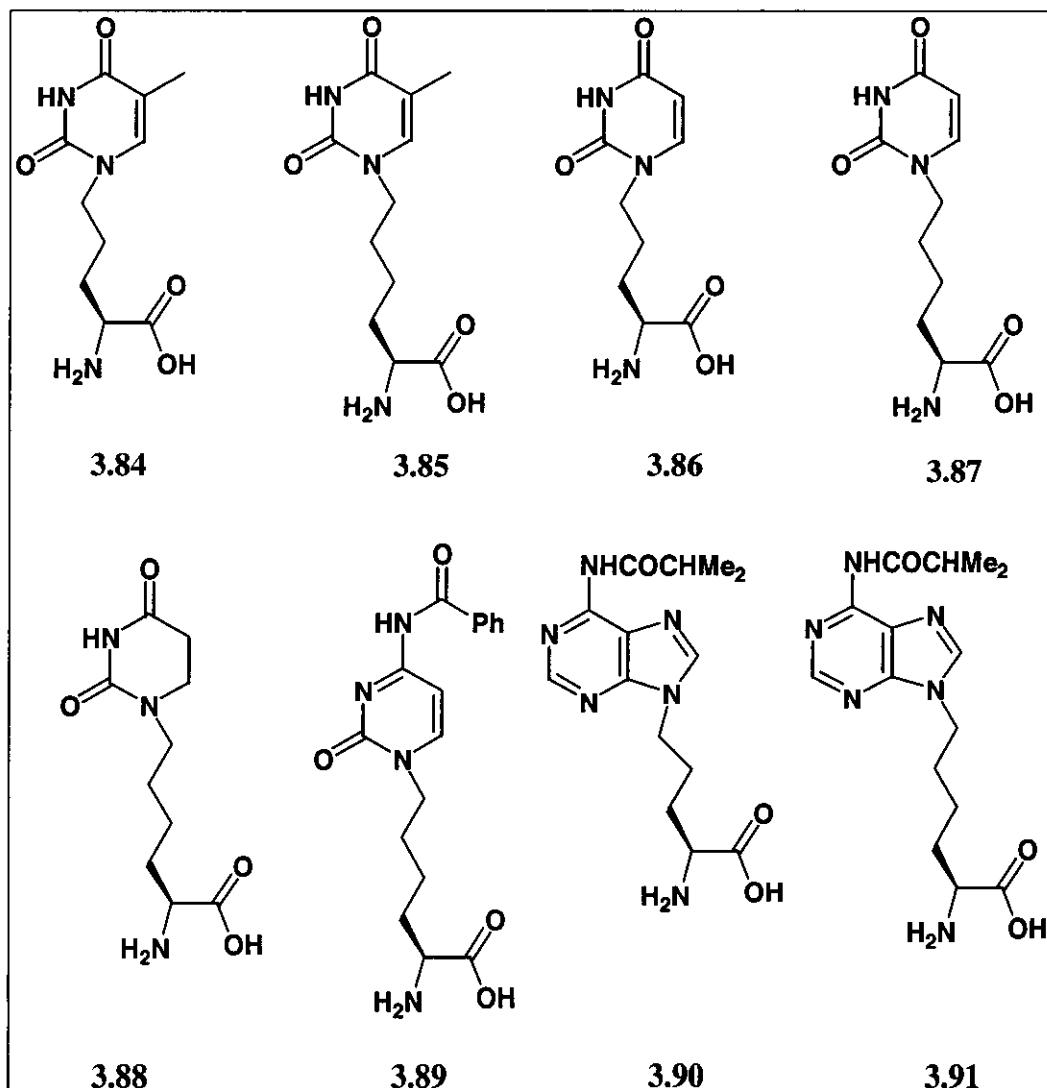
To afford the corresponding parent amino acid and to monitor the stereochemical integrity of the synthesis, the Z-protecting group was removed using catalytic hydrogenation with 10% Pd on C (Scheme 3.49).



Scheme 3.49

Our initial attempts at hydrogenation using ethyl acetate as solvent were unsuccessful due to solubility problems with both the Z-protected and final amino acid. Similarly, glacial acetic acid and methanol were also tried, but with no success.

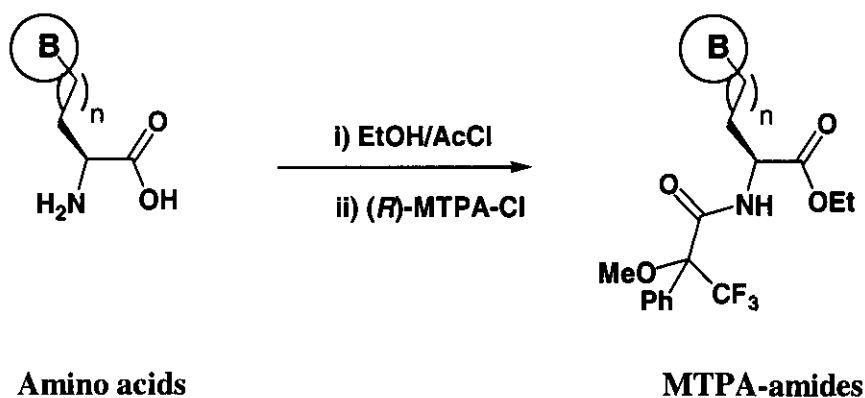
Eventually, it was found that a solution of ethanol/water in a ratio of 7/3 v/v gave the best results. Most of the Z-protected amino acids previously described were submitted to catalytic hydrogenation to afford the novel amino acids shown below.



In general, the catalytic hydrogenation proceeded in good yield, from 61% for **3.88** to 90% for **3.84**. While the amino acid **3.87** was obtained after hydrogenolysis of the Z-amino acid **3.77** after 5 h, it was found that prolonged hydrogenolysis of **3.77** for 16 h led to the 5,6-dihydrouracil amino acid **3.88** in 88% yield.

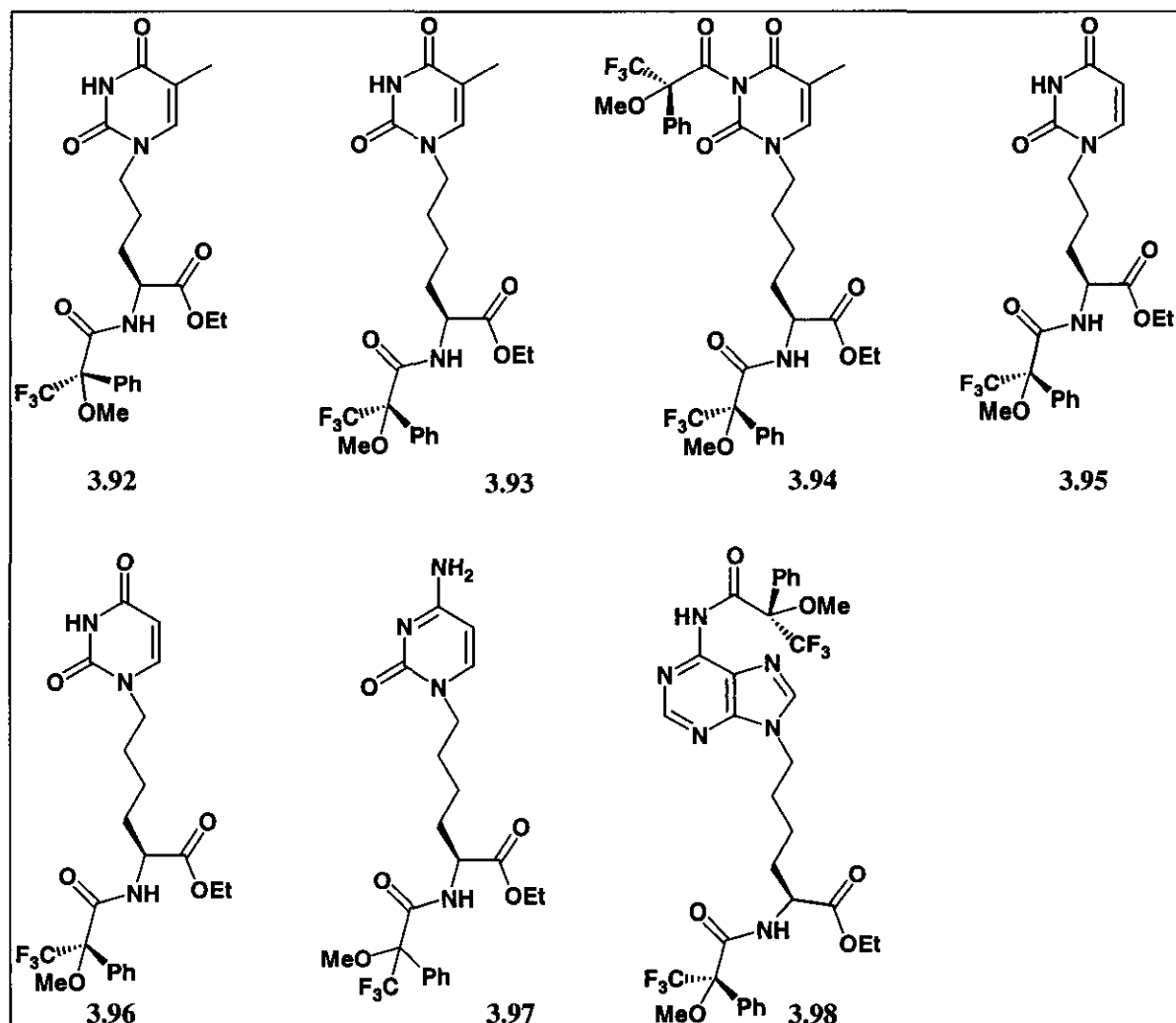
3.2.6 Determination of stereoselectivity

The enantiomeric excess of most of the amino acids was determined through the formation of the Mosher amide (Scheme 3.50).



Scheme 3.50

The amino acids (50 mg) were first converted to their corresponding ethyl ester hydrochloride by slow addition of acetyl chloride to a solution of the amino acids in ethanol at 0°C. The crude ethyl ester hydrochlorides were then coupled to (*R*)-MTPA-Cl (100mg) in DCM and excess triethylamine. The Mosher amides so-produced were isolated and characterised. Their structures are shown below.



One problem we encountered was that some amino acids underwent diamide formation (e.g. **3.90** and **3.91**, and **3.95**). However, we found that this allowed us to cross check enantiomeric purity, because both monoamide and diamide were able to report on stereoselectivity. In the ^1H NMR spectra of the Mosher amide derivatives a major and a minor diastereoisomer were observed in some cases. This was noted especially by the presence of a major and a minor singlet corresponding to the methoxy group of the Mosher amide. Subsequent analysis of the CF_3 signals in the ^{19}F NMR spectra (see appendix) revealed very good enantiomeric excesses for the amino acids **3.84** (85%), **3.85** (88%), **3.86** (88%), **3.87** (89%) and **3.91** (86%) (Table 3.8). In the case of the amino acid **3.91** the reaction to form the Mosher amide **3.98** removed the 2-methylpropionyl group from the *N9* of adenine, presumably by ethanolysis during esterification, leading to the diamide derivative.

One outstanding issue remains for the synthesis of cytosinyl amino acid **3.89**. We were unable to isolate the corresponding Mosher amide for spectroscopic identification, though an ^{19}F NMR analysis of the crude amide revealed only two singlets and an e.e. of 81%.

Amino acids	Amides	e.e. (%)
3.84	3.92	85
3.85	3.93, 3.94*	88, 88*
3.86	3.95	88
3.87	3.96	89
3.89	3.97	81
3.91	3.98	86*

*e.e. measured from corresponding diamide

Table 3.8

3.2.7 Conclusion and further work

The radical methodology has enabled us to make available a range of novel optically active pyrimidinyl and purinyl amino acids. Indeed, we have shown that pyrimidinyl (thymine and uracil) and purinyl (adenine and guanine) radicals could undergo diastereoselective conjugate addition onto an oxazolidinone acceptor. The Z-protected amino acids could be easily accessed in good yield by base hydrolysis of the oxazolidinone adducts. We were also able to vary the distance from the glycine backbone to the nucleic acid base. Moreover, the corresponding amino acids were synthesised with good enantiomeric purity (85 to 89 % e.e.).

Work that remains outstanding from the current project is (1) improvement in the yield of the amino acid bearing the cytosine nucleobase, (2) unmasking of the Z-protected guanine-containing amino acid to give the free amino acid, and (3) synthesis of the lower guanine-containing homologue that has a three-carbon spacer between the nucleobase and the amino acid backbone.

Future developments of the project are as follows. Although we have found the conjugate radical addition to be general, the conditions of the radical addition nevertheless require detailed investigation to improve the ratio of the desired conjugate addition to unwanted reduced products. This could, for example, potentially be achieved by using a different radical initiator such as triethylborane in the presence of traces of oxygen. Another alternative would be to use different reducing agents like tris(trimethylsilyl)silane. It would also be interesting to replace the tin reagent by one containing another (semi)metal like germanium or mercury for example. There are various other radical generation protocols that might be explored. For example, the carbon-centred radical could be accessed *via* xanthate esters, selenium-containing precursors or Barton esters. The downside of this approach would be that it would involve a revision of the precursor synthesis.

Another potential extension to this work could be to add a nitrogen-centred (or oxygen-centred) radical onto the dehydroalanine acceptor, hence forming a carbon-nitrogen or carbon-oxygen bond instead of a carbon-carbon bond. This option would lead to a one-carbon spacer between the nucleobase and amino acid instead of the three- or four-carbon spacers generated by the current work.

Another, obvious extension of the work is to apply the radical addition to other heterocyclic precursors such as modified nucleobases (*e.g.* O6-methylguanine, thiouracil), (benz)imidazole, triazole, isoxazole, indole etc.

Other nitrogen protecting groups such as Boc, Fmoc, benzoyl could be used in lieu of the Z-protecting group on the oxazolidin-5-one acceptor, thereby avoiding the hydrogenation step.

The finding that *N*3-benzoyl-*N*1-(3-iodopropyl)uracil underwent intramolecular addition to form a bicyclic system could be exploited further by introducing more functional groups onto the radical precursor. This cyclisation could also be the basis for a cascade radical reaction leading to more complex fused ring systems. There is potential to develop this reaction into other natural product series away from the PNA area.

Finally, short PNA's could be designed from the synthesised amino acids bearing the nucleobases. Hybridisation studies using those new PNAs could then be carried out to study potential specific binding affinity with DNA or self-hybridisation.

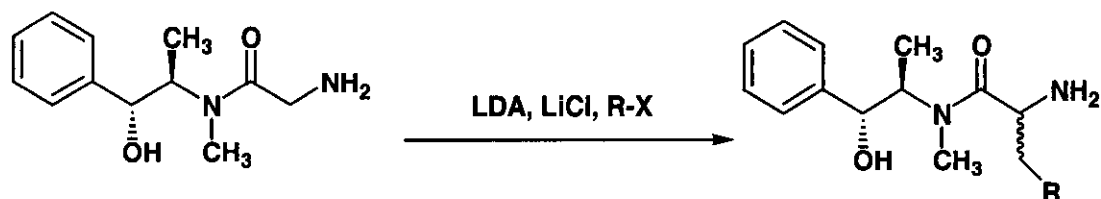
CHAPTER 4

EXPERIMENTAL

Experimental 1 Glycine enolate approach

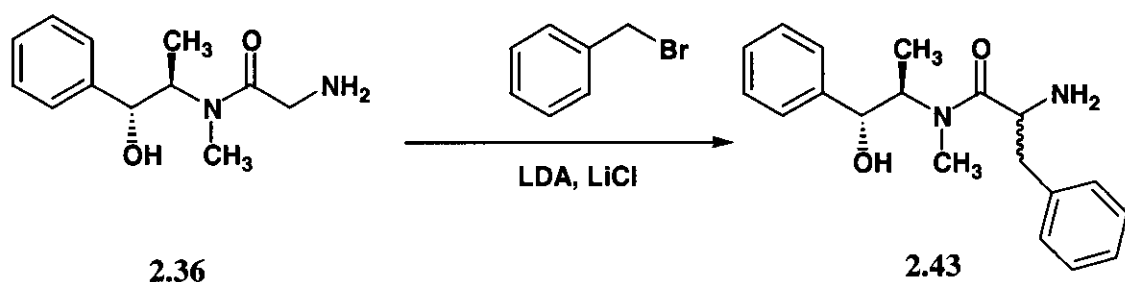
General Melting points were determined using a Pye 290 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1710 FTIR spectrophotometer. ^1H NMR spectra were recorded in deuteriochloroform (unless otherwise stated) on JEOL LAMBDA300 or JEOL EX400 spectrometers at 300 or 400 MHz, respectively, and chemical shifts are quoted in parts per million (p.p.m) from tetramethylsilane as internal standard. Coupling constants (J), where appropriate, are quoted in Hz with the following multiplicities; s-singlet, d-doublet, t-triplet, q-quartet and m-multiplet. The prefix br-broad is used where applicable. ^{13}C Spectra were recorded on the same instruments at 75 MHz or 100 MHz, respectively, in deuteriochloroform (unless otherwise stated) and chemical shifts are quoted in parts per million (p.p.m) from tetramethylsilane as internal standard. ^{19}F spectra were recorded on a JEOL EX400 spectrometer at 376 MHz using TFA as external standard. Low-resolution mass spectra were obtained using an AEI MS902 spectrometer in EI-positive mode. High-resolution EI/CI mass spectra were performed by the EPSRC National Mass Spectrometry Service in Swansea. Microanalytical data were obtained from Medac Ltd., Brunel Science Centre, Englefield Green, Egham, TW20 0BZ. Solvents were dried and distilled immediately before use: chloroform and DCM from CaH_2 , THF and toluene from K, using benzophenone as indicator; methanol and ethanol from Mg turnings and iodine. *n*-Butyllithium was titrated with diphenylacetic acid before use. Column chromatography was performed under medium pressure using silica gel (Kieselgel 60; 220-440 mesh). TLC analysis was carried out using Machery-Nagel Polygram SIL G/UV₂₅₄ plates on a plastic backing and visualised by ultraviolet light or aqueous potassium permanganate spray (KMnO_4 : K_2CO_3 : water, 6:1:100, w/w/v). Organic extracts were dried over anhydrous MgSO_4 .

General method for alkylation of pseudoephedrine glycineamide⁷²



A freshly prepared solution of LDA (2M, 1.95 equiv.) in hexanes was added over 0.25-0.5h to a stirred slurry of anhydrous pseudoephedrine glycineamide⁷⁰ (1.0 equiv.) and flame dried lithium chloride (6 equiv.) in THF under a positive argon atmosphere at 0°C. After stirring at 0°C for 0.5-1h, the haloalkane (1.1 equiv.) in THF was added dropwise. After 12h, hydrochloric acid (1M) was added to the solution, followed by ethyl acetate. The organic layer was extracted with a second portion of hydrochloric acid (1M). The aqueous extracts were combined, and the resulting solution was cooled in an ice bath and carefully basified to pH 14 by addition of 50% aqueous solution of sodium hydroxide. The basic aqueous solution was extracted with DCM. The combined organic extracts were combined and dried over potassium carbonate, filtered and concentrated in *vacuo* to provide the alkylated products.

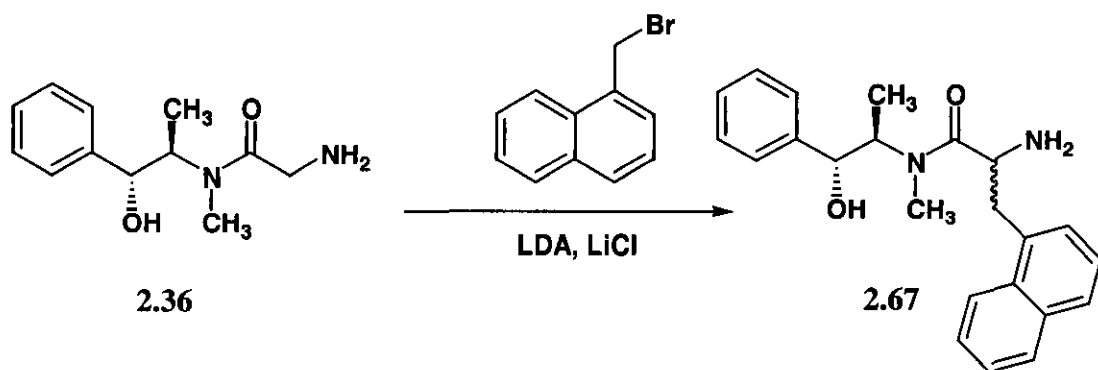
(1R, 2R, 2'S)-2'-Amino-3'-phenylpropanoylpseudoephedrine, 2.43⁷²



Prepared as above using LDA (2M, 17.56 ml, 0.035 mol), (1R,2R)-pseudoephedrine glycineamide (4g, 0.018 mol) and lithium chloride (4.58g, 0.108 mol) in THF (100 ml), together with benzyl bromide (3.39g, 0.02 mol) in THF (10ml). After 2h, hydrochloric acid (1M, 100ml) was added to the clear solution, followed by ethyl acetate (200ml). The

organic layer was extracted with a second portion of hydrochloric acid (1M, 100ml). The aqueous extracts were combined, cooled, basified and extracted with DCM (3×80ml). Removal of the solvent provided a hygroscopic solid residue (3.45g, 62%), $R_f=0.53$ (DCM:MeOH:Et₃N, 90:5:5, v/v/v); Found: MH^+ (ES^+) 313.1908. C₁₉H₂₄N₂O₂ requires: MH 313.1916; ν_{max}/cm^{-1} (KBr) 3300, 3250, 1625, 1500, 1450, 1400, 1300, 1100; δ_H (4:1 rotamer ratio, the asterisk denotes the minor isomer) 0.88 and 0.99* (3H, d, J 6.2, CHCH₃), 2.6 and 2.9* (3H, s, NCH₃), 2.7- 2.82 (2H, 2 × dd, J 13.2 and 7.2, CHCH₂), 3.7 (1H, t, J 7.1, CHCH₂), 4.3 and 4.45* (1H, d, J 6.6, CHOH), 4.6 and 4.0* (1H, m, CHCH₃), 7.0-7.3 (10H, m, Ar); δ_C 14.4 and 15.5* (CHCH₃), 27.1* and 30.4 (NCH₃), 41.9* and 30.4 (CH₂), 53.2 (CHCH₂), 56.5 and 57.9* (CHCH₃), 75.0* and 75.6 (CHOH), 126.5, 126.6, 126.7, 126.8, 127.7, 128.2, 128.3, 128.4, 128.5, 128.6, 129.2, 129.4 (6 × Ar and 6 × Ar*), 137.5 and 138.4* (ArC), 141.7* and 142.0 (ArC), 175.2* and 176.2 (C=O); m/z (CI) 313 (MH^+ , 100%), 295 (40), 277 (25), 267 (15), 255 (60), 231 (30).

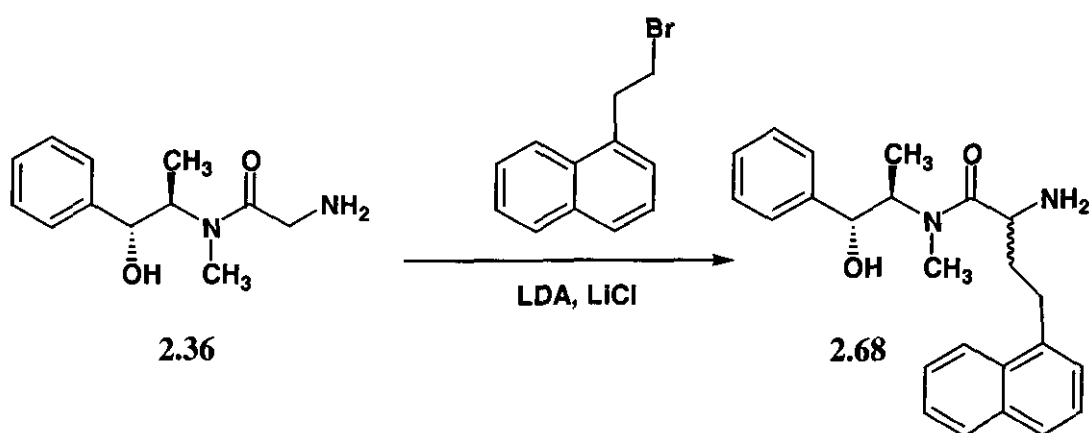
(1R, 2R, 2'S)-2'-Amino-3'-(1-naphthyl)propanoylpseudoephedrine, 2.67



Prepared by the general method, using (1R,2R)-pseudoephedrine glycinamide (2 g, 9 mmol), LDA (8.78 ml, 18 mmol), lithium chloride (2.29 g, 54 mmol) and 1-(bromomethyl)naphthalene (1.67 g, 9.5 mmol). After the usual extraction, the yellow gum was purified by column chromatography (DCM:MeOH:Et₃N, 90:5:5, v/v/v) to yield the *title compound* as a yellow hygroscopic gum (1.98 g, 61%). Found: MH^+ (ES^+) 363.2076. C₂₃H₂₆N₂O₂ requires: MH 363.2072. ν_{max}/cm^{-1} (film) 3400, 3200, 2850, 1650, 1300, 950; δ_H (4:1 rotamer ratio, the asterisk denotes the minor isomer) 0.90 and 1.0* (3H, d, J 4.9, CHCH₃), 2.6 (3H, s, NCH₃), 3.1 and 3.2 (2H, 2 × dd, J 5.4 and 9.9,

CHCH₂), 3.8 and 3.9* (1H, t, *J* 5.4, CHCH₂), 4.15* and 4.4 (1H, m, CHCH₃), 4.1 and 4.2* (1H, d, *J* 6.7, CHOH), 6.9-7.9 (12H, m, Ar); δ_C 15.2 and 15.6* (CHCH₃), 29.8* and 30.8 (NCH₃), 39.4 and 39.5* (CH₂), 52.2 and 56.9* (CHCH₂), 53.7 and 68.9* (CHCH₃), 75.6 and 75.5* (CHOH), 123.3, 123.4, 125.3, 125.4, 125.6, 126.1, 126.2, 126.3, 126.7, 126.8, 127.4, 127.5, 127.7, 128.1, 128.3, 128.4, 128.8, 128.9, 131.9 and 132.0 (10 × Ar and 10 × Ar*), 132.2 and 133.6* (quaternary C), 133.8 and 134.2* (quaternary C), 135.1 and 135.3* (quaternary C), 141.9 and 142.0* (quaternary C), 176.3* and 176.4 (C=O); *m/z* (CI) 363 (MH⁺, 100%), 230 (20) and 166 (100).

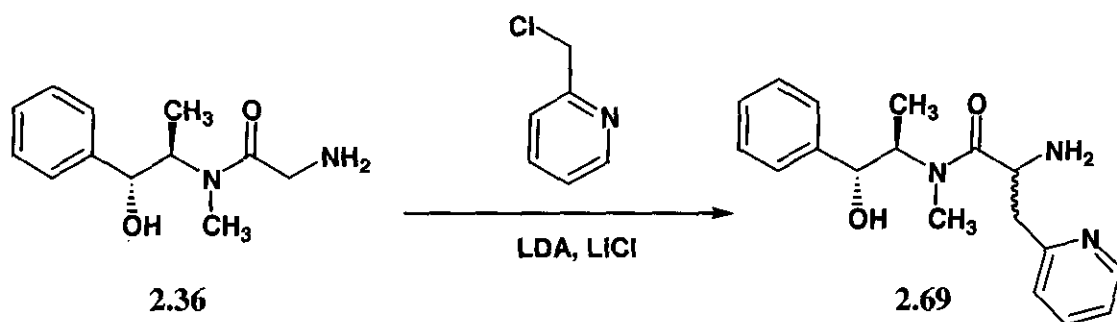
(1*R*, 2*R*, 2'*S*)-2'-Amino-4'-(1-naphthyl)butanoylpseudoephedrine, 2.68



Prepared by the general method, using (1*R*,2*R*)-pseudoephedrine glycinamide (1.51 g, 6.77 mmol), LDA (6.60 ml, 13.21 mmol), lithium chloride (1.73 g, 40.64 mmol) and 1-(2-bromoethyl)naphthalene (1.75 g, 7.45 mmol). After the usual extraction, the yellow hygroscopic gum was purified by column chromatography (DCM:MeOH:Et₃N, 90:5:5, v/v/v), to yield the title compound as yellow gum (0.85 g, 33%): ν_{max}/cm⁻¹ (film) 3400, 3050, 3000, 1650, 1450, 1250, 750; δ_H (4:1 rotamer ratio, the asterisk denotes the minor isomer) 0.65* and 0.80 (3H, d, *J* 4.9, CHCH₃), 1.6-1.75 (2H, m, CH₂), 2.4 (3H, s, NCH₃), 2.95-3.05 (2H, m, CH₂), 3.40 and 3.65* (1H, m, CHCH₂), 3.8* and 4.35 (1H, m, CHCH₃), 4.4 (1H, m, CHOH), 7.0-7.35 (9H, m, Ar), 7.6 (1H, d, *J* 5.4, Ar), 7.7 (1H, d, *J* 5.4, Ar), 7.85 and 8.1* (1H, d, *J* 5.4, Ar). δ_C 14.0 and 15.5* (CHCH₃), 29.0 (CH₂), 31.0*

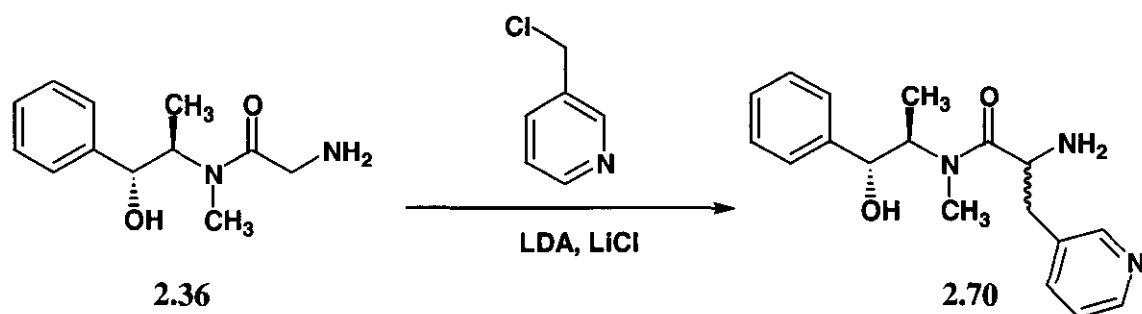
and 46.0 (NCH₃), 35.0 and 36.0* (CH₂), 51.0 (CHCH₂), 63.0 and 75.0* (CHOH), 57.0* and 75.4 (CHCH₃), 123.54, 123.69, 123.98, 125.35, 125.65, 125.72, 125.97, 126.05, 126.19, 126.36, 126.65, 126.98, 127.46, 127.60, 127.82, 127.91, 128.13, 128.26, 128.48 and 128.59 (10 × Ar and 10 × Ar*), 131.6 and 131.8* (quaternary C), 133.7 (quaternary C), 137.4 and 138.0* (quaternary C), 141.7* and 142.1 (quaternary C), 175.9* and 176.8 (C=O); *m/z* 377 (CI) (MH⁺, 70%), 355 (60) and 337 (80).

(1*R*, 2*R*, 2'*S*)-2'-Amino-3'-(2-pyridyl)propanoylpseudoephedrine, 2.69



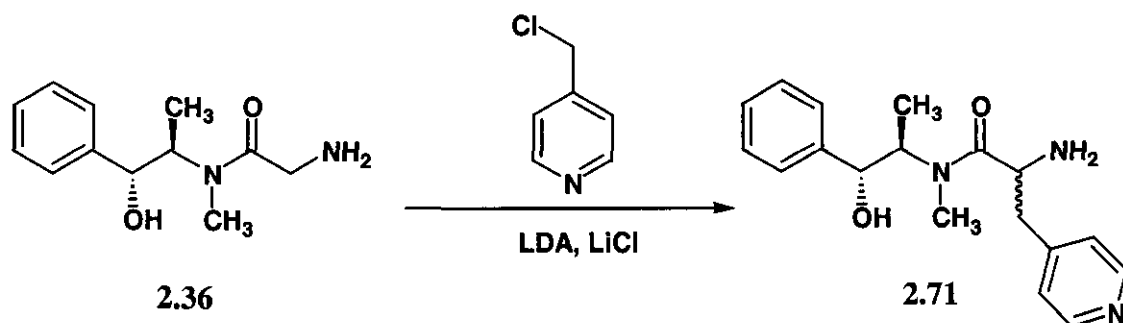
2-Chloromethylpyridine hydrochloride (5g, 30.5 mmol) and triethylamine (3.1 g, 30.5 mmol) were stirred for 3 h at room temperature in dry THF (100 ml) under an atmosphere of nitrogen. The triethylamine hydrochloride salt was filtered off and the solution reduced to 20 ml in *vacuo* and used immediately in the alkylation. The alkylated compound was prepared following the general method, using (1*R*,2*R*)-pseudoephedrine glycinamide (5.64 g, 25.4 mmol), lithium chloride (6.46 g, 152.4 mmol), LDA (24.4 ml, 48.8 mmol) and 2-chloromethylpyridine (3.89 g, 30 mmol). The crude brown gum (6.2 g) that was obtained was subjected several times to column chromatography (DCM:MeOH:Et₃N, 90:5:5, v/v/v) to yield the title compound (4.95 g, 62%) which was used directly in the next step.

(1*R*, 2*R*, 2'*S*)-2'-Amino-3'-(3-pyridyl)propanoylpseudoephedrine, 2.70



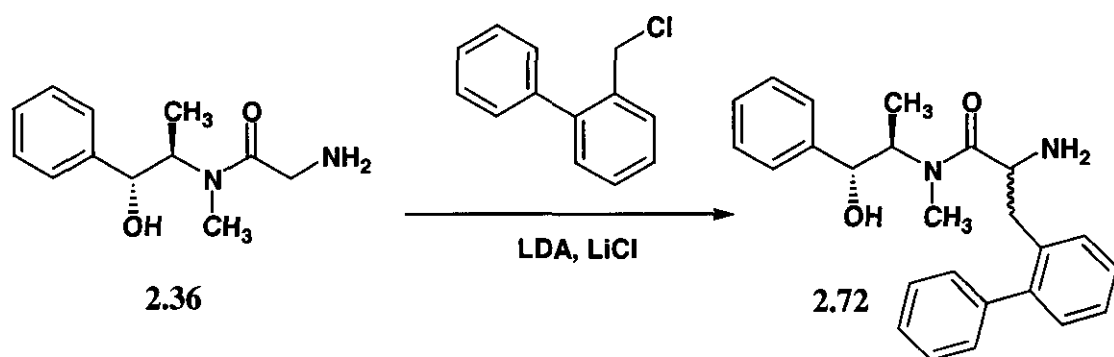
3-Chloromethylpyridine hydrochloride (3g, 18.3 mmol) and triethylamine (1.85 g, 18.3 mmol) were stirred for 3 h at room temperature in dry THF (100 ml) under an atmosphere of nitrogen. The triethylamine hydrochloride salt was filtered off and the solution reduced to 20 ml in *vacuo* and used immediately in the alkylation. The alkylated compound was prepared following the general method, using (1*R*,2*R*)-pseudoephedrine glycinamide (3.4 g, 15.3 mmol), lithium chloride (3.89 g, 91.8 mmol), LDA (14.9 ml, 29.8 mmol) and 3-chloromethylpyridine (2.33 g, 18.3 mmol). The brown gum that was obtained was subjected several times to column chromatography (DCM:MeOH:Et₃N, 90:5:5, v/v/v) to yield the title compound (2.65 g, 55%) which was used directly in the next step.

(1*R*, 2*R*, 2'*S*)-2'-Amino-3'-(4-pyridyl)propanoylpseudoephedrine, 2.71



4-Chloromethylpyridine hydrochloride (3g, 18.3 mmol) and triethylamine (1.85 g, 18.3 mmol) were stirred for 3 h at room temperature in dry THF (100 ml) under an atmosphere of nitrogen. The triethylamine hydrochloride salt was filtered off and the solution reduced to 20 ml in *vacuo* and used immediately for the alkylation. The alkylated compound was prepared following the general method, using (1*R*,2*R*)-pseudoephedrine glycineamide (2.96 g, 13.3 mmol), lithium chloride (3.4 g, 80.2 mmol), LDA (13 ml, 26.0 mmol) and 4-chloromethylpyridine (2.04 g, 16.0 mmol). The black gum that was obtained was subjected several times to column chromatography (DCM:MeOH:Et₃N, 90:5:5, v/v/v) to yield the title compound as a brown hygroscopic solid (1.5 g, 36%) which was used directly in the next step.

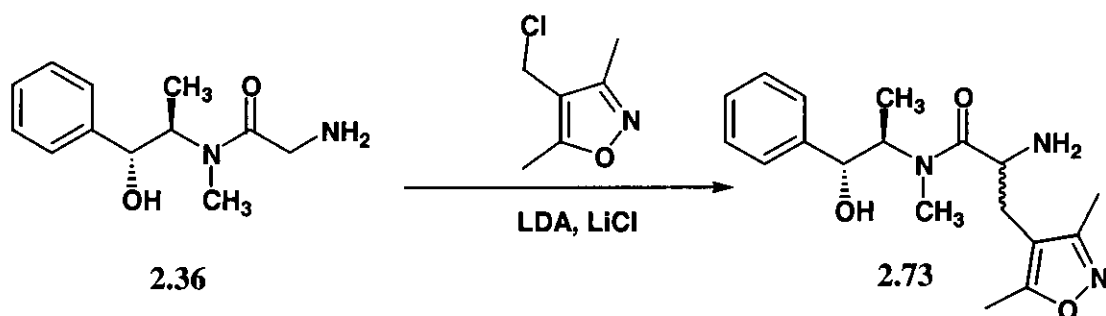
(1*R*, 2*R*, 2'*S*)-2'-Amino-3'-(2-phenylphenyl)propanoylpseudoephedrine, 2.72



Prepared following the general method using (1*R*,2*R*)-pseudoephedrine glycineamide (2.50 g, 11.3 mmol), lithium chloride (2.86 g, 67.5 mmol), LDA (10.9 ml, 21.8 mmol) and 2-phenylchloromethylbenzene (3.06 g, 12.4 mmol) to yield the *title compound* as a white hygroscopic powder (2.97 g, 68%). Found: MH⁺ (ES⁺) 389.2234. C₂₅H₂₈N₂O₂ requires: MH 389.2229. $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3100, 3000, 1250, 750, 700; δ_{H} (4:1 rotamer ratio, the asterisk denotes the minor isomer) 0.60* and 0.90 (3H, d, *J* 4.9, CHCH₃), 2.0 (3H, s, NCH₃), 2.4 and 2.8 (2H, 2 × dd, *J* 8.7 and 11.7, CH₂), 3.3 and 3.4* (1H, m, CHCH₂), 3.2 (1H, m, CHCH₃), 4.40 (1H, d, *J* 6.3, CHOH) 7.1-7.4 (14H, m, Ar); δ_{C} 14.1* and 14.2 (CHCH₃), 31.0 (NCH₃), 39.2* and 39.5 (CHCH₂), 50.6* and 51.8 (CHCH₂), 74.8* and 75.0 (CHOH), 75.4 (CHCH₃), 126.0, 126.1, 126.3, 126.8, 126.9, 127.2, 127.4,

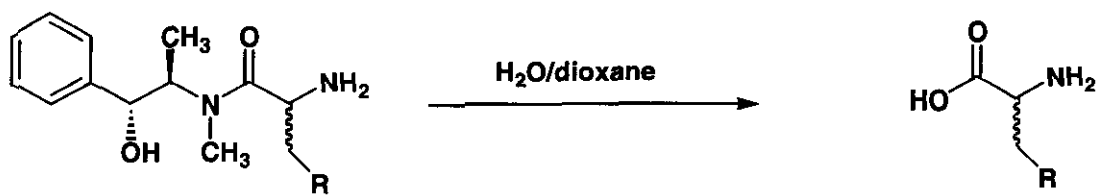
127.5, 127.6, 128.2, 128.4, 128.6, 128.8, 129.1, 129.3, 130.2, 130.4, 130.5, 130.6, 131.0 (10 × Ar and 10 × Ar*), 132.0 and 132.3* (quaternary C), 133.0 and 133.2* (quaternary C), 141.0 and 141.2* (quaternary C), 141.9* and 142.2 (quaternary C), 175.0* and 176.1 (C=O); m/z (CI) 389 (MH^+ , 40%), 166 (100) and 58 (15).

(1*R*, 2*R*, 2'*S*)-2'-Amino-3'-(3,5-dimethylisoxazol-4-yl)propanoylpseudoephedrine, 2.73



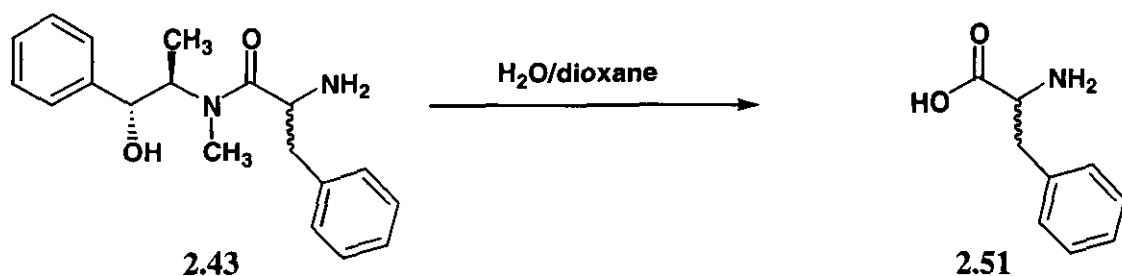
Prepared following the general method using (1*R*,2*R*)-pseudoephedrine glycinamide (5.88 g, 26.5 mmol), lithium chloride (6.73 g, 159 mmol), LDA (25.8 ml, 51.6 mmol) and 4-(chloromethyl)-3,5-dimethylisoxazole (4.24 g, 29.1 mmol) to yield a white hygroscopic powder (8.46 g, 97%). Found: MH^+ (ES^+) 332.1976. $C_{18}H_{25}N_3O_3$ requires: MH 332.1974. ν_{max}/cm^{-1} (film) 3390, 2950, 2900, 1650, 1450, 1400, 1250, 1200, 1050, 750, 700; δ_H (4:1 rotamer ratio, the asterisk denotes minor rotamer peaks) 0.66* and 0.77 (3H, d, J 4.8, $CHCH_3$), 2.05* and 2.1 (3H, s, isoxazole CH_3), 2.15* and 2.25 (3H, s, isoxazole CH_3), 2.35 and 2.45 (2H, 2 × dd appears as multiplets, $CHCH_2$), 2.65 (3H, s, NCH_3), 3.6 and 3.8* (1H, m, $CHCH_2$), 4.3* and 4.4 (1H, d, J 6.6, $CHOH$), 4.64 (1H, m, $CHCH_3$), 7.19-7.27 (5H, m, ArCH); δ_C 10.0 and 10.5* (isoxazole CH_3), 11.0 and 11.5* (isoxazole CH_3), 14.0 and 14.5* ($CHCH_3$), 28.0 and 28.5* ($CHCH_2$), 31.0 (NCH_3), 51.0 and 51.5* ($CHCH_2$), 55.8 ($CHCH_3$), 75.0 and 75.5* ($CHOH$), 109.5 and 110.0* (quaternary ArC), 126.3, 126.5, 126.6, 126.7, 126.9, 127.6, (3 × Ar and 3 × Ar*), 141.0 and 141.5*, 159.0 and 159.5*, 166.0 and 166.5* (3 × quaternary ArC), 175.0* and 176.0 (C=O); m/z (CI) 332 (MH^+ , 100%), 166 (65), 112 (18), and 58 (20).

General method for the hydrolysis of alkylated pseudoephedrine glycnamides⁷²



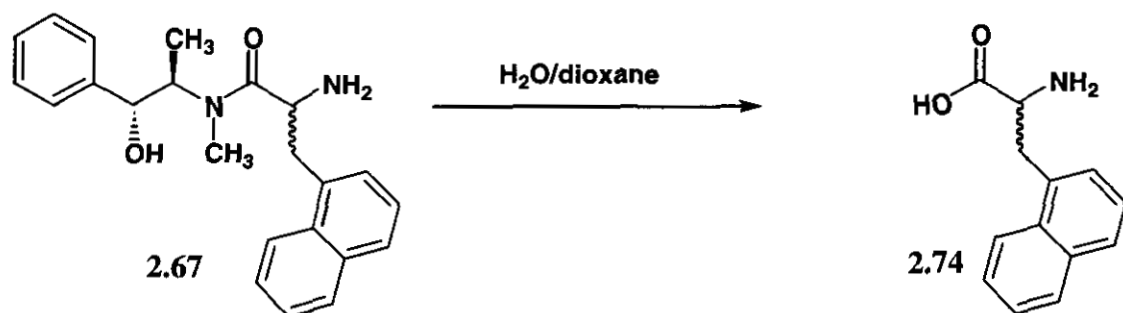
The alkylated pseudoephedrine glycnamide was dissolved in the minimum volume of dioxane and water was added. The solution was then heated at reflux for 12h, cooled to 20°C and diluted with water. This solution was extracted with DCM (2×25 ml). The combined organic extracts were extracted with water. The aqueous layers were combined and concentrated *in vacuo* to afford a white solid. The solid was triturated in ethanol to remove residual pseudoephedrine, filtered and dried *in vacuo* to give the free amino acid. The combined organic extracts were dried over potassium carbonate, filtered, and concentrated to afford pseudoephedrine.

Phenylalanine, 2.51⁷²



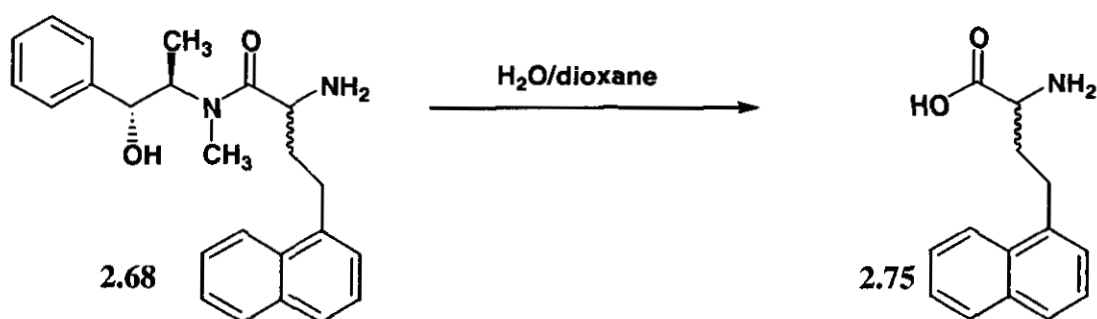
Prepared following the general method, using **2.43** (2g, 6.4 mmol) in dioxane (5ml) and water (25 ml). Work-up afforded the title compound (0.81g, 76%) and pseudoephedrine, (1.0g, 70%); δ_{H} (D_2O) 2.95 and 3.15 (2H, $2 \times \text{dd}$, J 8.0, 14.5 and 5.1, CH_2), 3.83 (1H, dd, J 8.0 and 5.2, CHCH_2), 7.16-7.26 (5H, m, Ar); δ_{C} (D_2O) 37.15 (CH_2), 56.83 (CH), 128.49, 129.90, and 130.16 ($3 \times \text{ArCH}$), 135.90 (ArC), 174.74 (C=O).

2-Amino-3-(1-naphthyl)propanoic acid, 2.74



Prepared following the general method, using **2.67** (0.36g, 4.1 mmol) in dioxane (2ml) and water (10 ml). Work-up afforded pseudoephedrine (0.11g, 50%) and the title compound (0.16g, 76%). M.p. 185-186°C (lit.¹⁰⁵ m.p. 179°C); Found: MH^+ (ES^+) 216.1022. $\text{C}_{13}\text{H}_{13}\text{NO}_2$ requires: MH 216.1024; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3100, 2600, 2300, 1675, 1600, 1500, 1400, 1350, 1150, 800, 750; δ_{H} (D_2O) 3.17 and 3.78 (2H, 2 × dd, J 5.3, 8.50 and 14.5, CH_2), 3.95 (1H, dd, J 5.3 and 8.5, CH), 7.33-7.89 (7H, m, Ar); m/z (CI) 216 (MH^+ , 20%), 170 (100) and 145 (40).

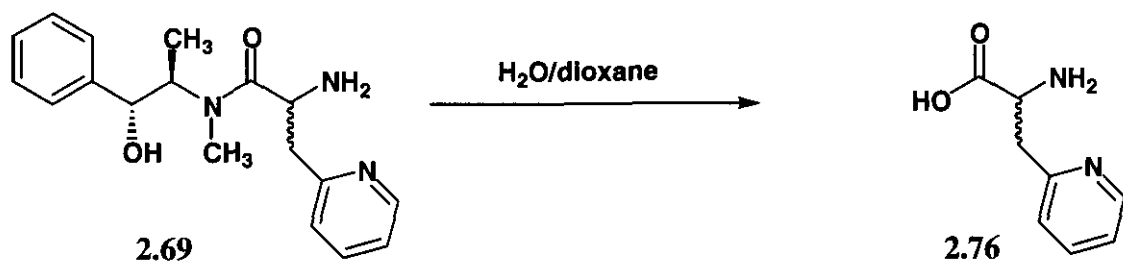
2-Amino-4-(1-naphthyl)butanoic acid, 2.75



Prepared following the general method, using **2.68** (0.75g, 4.2 mmol) in dioxane (5ml) and water (20 ml). Work-up afforded the *title compound* (0.34g, 74%) as a hygroscopic solid and pseudoephedrine (0.19g, 58%), Found: MH^+ (ES^+) 230.1181. $\text{C}_{14}\text{H}_{15}\text{NO}_2$ requires: MH 230.1181; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3150, 2600, 2350, 1670, 1620, 1500, 1410, 1350, 1150, 850; δ_{H} (D_2O) 2.15 (2H, m, CHCH_2), 3.2 (2H, m, CH_2), 3.8 (1H, t, J 7.2,

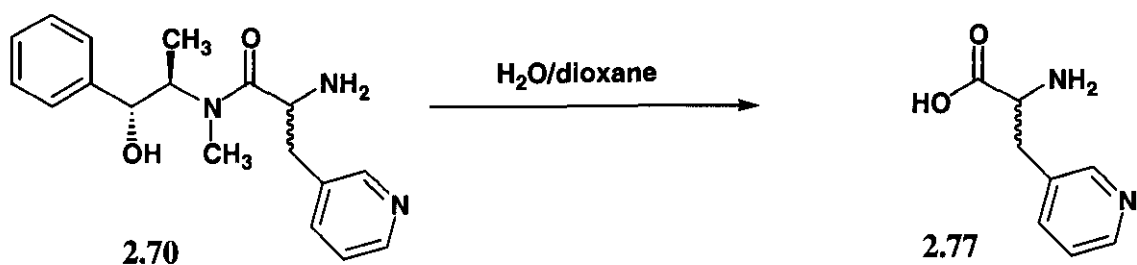
CHCH_2), 7.30-7.80 (7H, m, ArH); m/z 229 (EI) (M^+ , 12%), 167 (50), 141 (100) and 115 (50).

2-Amino-3-(2-pyridyl)propanoic acid, 2.76



Prepared following the general method, using **2.69** (1.15g, 3.67 mmol) in dioxane (5ml) and water (20 ml). Work-up afforded the title compound (0.36g, 59%). M.p. 206-209°C (lit.¹⁰⁶ 210-211°C). Found: MH^+ (ES^+) 167.0820. $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$ requires: MH 167.0820; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3400, 2950, 2850, 2500, 1600, 1450, 1050; δ_{H} (D_2O) 3.30 and 3.45 (2H, 2×dd overlapped, J 5.0, 7.6, and 14.0, CHCH_2), 4.2 (1H, dd, J 5.0 and 7.6, CHCH_2), 7.40 (2H, m, pyridyl H3 and H5), 7.85 (1H, m, pyridyl H4), 8.60 (1H, m, pyridyl H6). m/z (CI) 167 (MH^+ , 3%), 148 (5), 121 (80), 93 (100) and 78 (15).

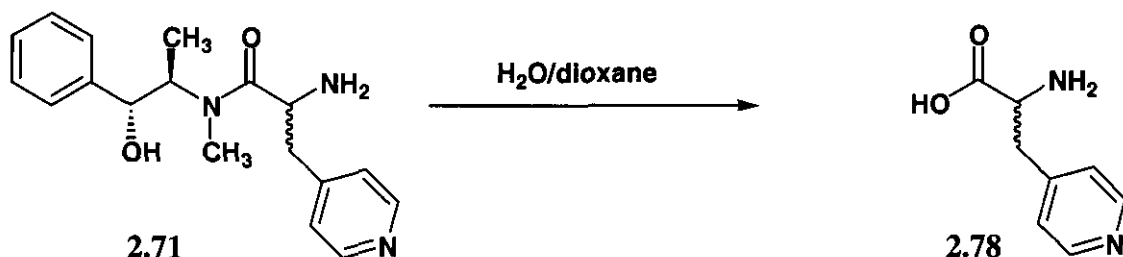
2-Amino-3-(3-pyridyl)propanoic acid, 2.77



Prepared following the general method using **2.70** (1.0g, 3.66mmol) in dioxane (5ml) and water (20 ml). Work-up afforded the title compound (0.26g, 49%). M.p. 253-254°C (lit.¹⁰⁶ 253-256°C). Found: MH^+ (ES^+) 167.0820. $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$ requires: MH 167.0820;

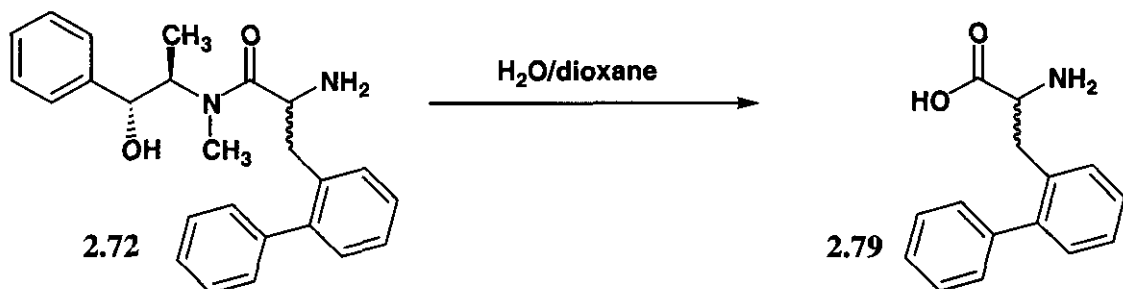
$\nu_{\max}/\text{cm}^{-1}$ (KBr) 3400, 2900, 2800, 2500, 1600, 1400, 1050; δ_{H} (D_2O) 3.15 and 3.25 (2H, $2 \times \text{dd}$ overlapped, J 14.8, 5.6 and 7.5, CHCH_2), 4.05 (1H, dd, J 5.6 and 7.5, CHCH_2), 7.38 (1H, m, pyridyl H5), 7.73 (1H, m, pyridyl H4), 8.38-8.40 (2H, m, pyridyl H2 and H6). m/z (CI) 167 (MH^+ , 30%), 121 (100), 93 (40) and 52 (38).

2-Amino-3-(4-pyridyl)propanoic acid, 2.78



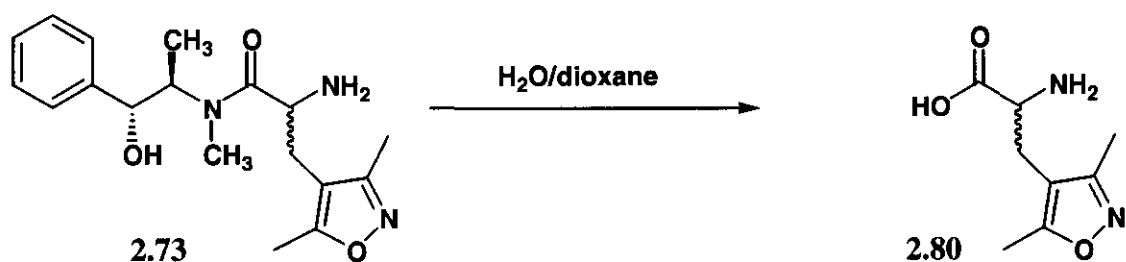
Prepared following the general method, using **2.71** (1.0g, 3.66mmol) in dioxane (5ml) and water (20 ml). Work-up afforded the title compound (0.21g, 40%). M.p. 239-241°C (lit.¹⁰⁶ 246-248°C). Found: MH^+ (ES^+) 167.0821. $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$ requires: MH 167.0820; $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3350, 2900, 2750, 2500, 2200, 1600, 1400, 1300, 1050; δ_{H} (D_2O) 3.06 and 3.12 (2H, $2 \times \text{dd}$, J 5.9, 7.5 and 14.5, CHCH_2), 4.05 (1H, dd, J 5.9 and 7.5, CHCH_2), 7.24-7.40 (4H, m, pyridyl H); δ_{C} (D_2O) 38.3 (CH_2), 57.6 (CHCH_2), 128.4 and 130.4 ($2 \times \text{ArCH}$), 137.3 (quaternary C), 174.0 (C=O); m/z (EI) 166 (M^+ , 100%), 150 (5), 121 (12), 88 (5) and 52 (28).

2-Amino-3-(2-phenylphenyl)propanoic acid, 2.79



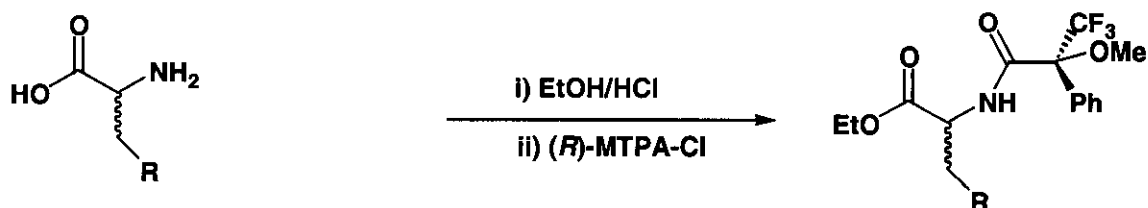
Prepared following the general method, using **2.72** (1.54g, 3.95 mmol) in dioxane (5ml) and water (20 ml). Work-up afforded pseudoephedrine (0.69, 78%) and the *title compound* (0.46g, 48%). M.p. 190-191°C. Found: MH^+ (ES^+) 242.1189. $\text{C}_{15}\text{H}_{15}\text{NO}_2$ requires: MH 242.1181; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3400, 3000, 1600, 1500, 1450, 1400, 1350, 1150, 800, 750, 700; δ_{H} (D_2O) 2.9 (1H, dd, J 7.2 and 10.8, CH_2), 3.62 (1H, dd, J 3.9 and 11.1, CH_2), 3.69 (1H, dd, J 3.9 and 7.2, CHCH_2), 7.3-7.6 (9H, m, Ar); δ_{C} (D_2O) 36.0 (CH_2), 56.4 (CHCH_2), 128.0, 128.3, 129.6, 129.7, 130.3, 130.8 and 131.7 (ArCH), 134.7, 142.5 and 144.1 (ArC), 173.83 ($\text{C}=\text{O}$); m/z (CI) 242 (MH^+ , 28%) and 196 (100).

2-Amino-3-(3,5-dimethylisoxazol-4-yl)propanoic acid, **2.80**



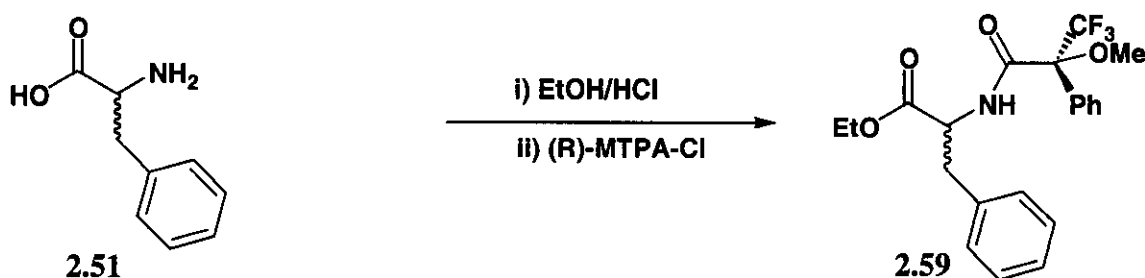
Prepared following the general method, using **2.73** (2.93g, 8.84 mmol) in dioxane (5 ml) and water (20 ml)). Work-up afforded pseudoephedrine (1.21, 62%) and the *title compound* (0.96g, 59%). M.p. 216-217°C. Found: MH^+ (ES^+) 185.0927. $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_3$ requires: MH 185.0926; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3400, 2950, 2600, 2050, 1650, 1500, 1450, 1400, 1200; δ_{H} (D_2O) 2.09 and 2.20 ($2 \times 3\text{H}$, $2 \times \text{s}$, isoxazole CH_3), 2.69-2.88 (2H, $2 \times \text{dd}$ overlapped, J 7.0 and 15.4, CH_2), 3.63 (1H, t, J 7.0, CH); δ_{C} (D_2O) 10.06 (CH_3), 11.08 (CH_3), 24.48 (CH_2), 55.05 (CH), 109.26, 161.86, and 169.16 ($3 \times \text{ArC}$), 174.22 ($\text{C}=\text{O}$); m/z (CI) 185 (MH^+ , 20%), 141 (50) and 124 (100).

General method for conversion of an amino acid into its (*S*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanamide (Mosher amide) derivative



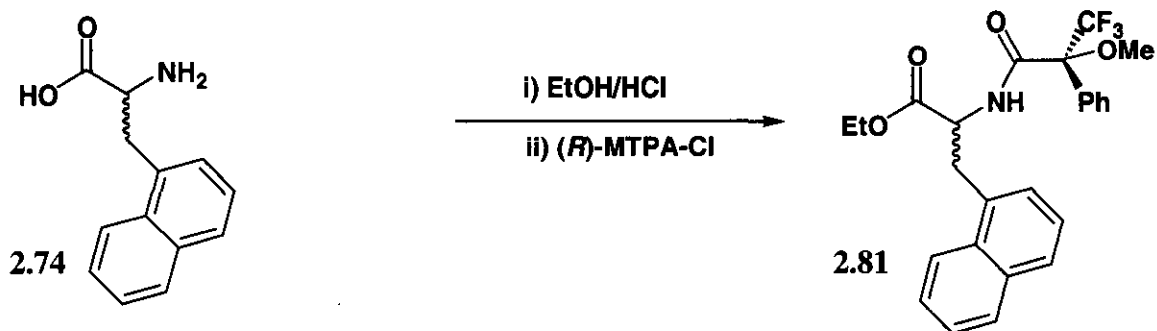
Acetyl chloride (10 mol equiv.) was added dropwise at 0°C to a stirred solution of the amino acid (~50 mg) in ethanol (~40 ml). The mixture was then stirred overnight at 25°C, heated at reflux for 4 h, cooled and the solvent evaporated under reduced pressure to give the ethyl ester hydrochloride salt which was further dried under vacuum overnight. (*R*)-2-Methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride (MTPA-Cl) (100 mg) was added dropwise at room temperature to the ester hydrochloride stirred in chloroform (4 cm³) and pyridine (4 cm³). The mixture was stirred overnight, water (20 cm³) was added and the mixture extracted with diethyl ether (3 x 20 cm³). The combined ethyl acetate layers were washed with saturated sodium hydrogen carbonate solution (3 x 10 cm³), dried (MgSO₄) and evaporated under reduced pressure to afford the product amide that was directly analysed by ¹⁹F NMR spectroscopy for the determination of enantiomeric purity.

(2'*S*)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-phenylpropanoate, 2.59



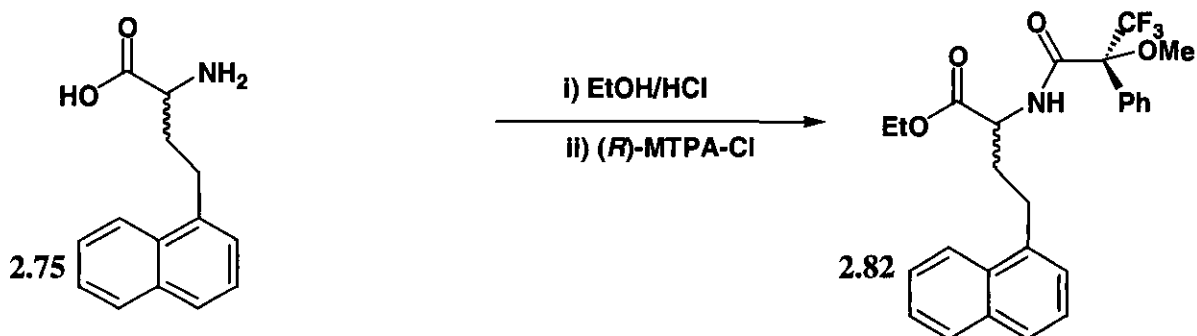
Prepared as above using **2.51** (~50 mg). δ_F -69.087 (major diastereoisomer, 93.5%), -69.141 (minor diastereoisomer, 6.5%); e.e. 87%.

(2'*S*)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(1-naphthyl)propanoate, 2.81



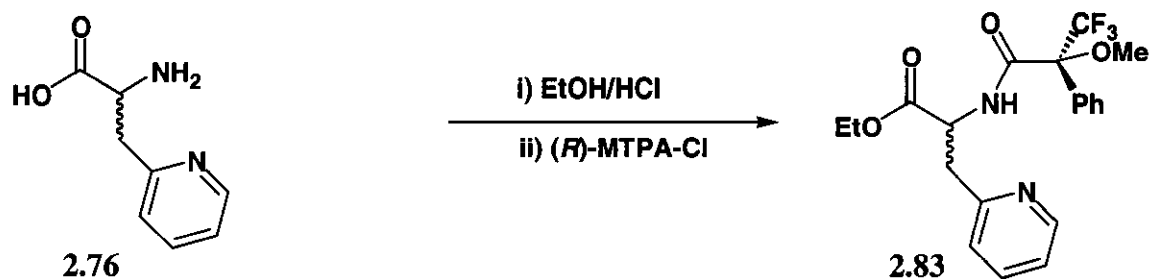
Prepared as above using **2.74** (~50 mg). δ_F -68.009 (major diastereoisomer, 93.5%), -68.085 (minor diastereoisomer, 6.5%); e.e. 87%.

(2'*S*)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-4-(1-naphthyl)butanoate, 2.82



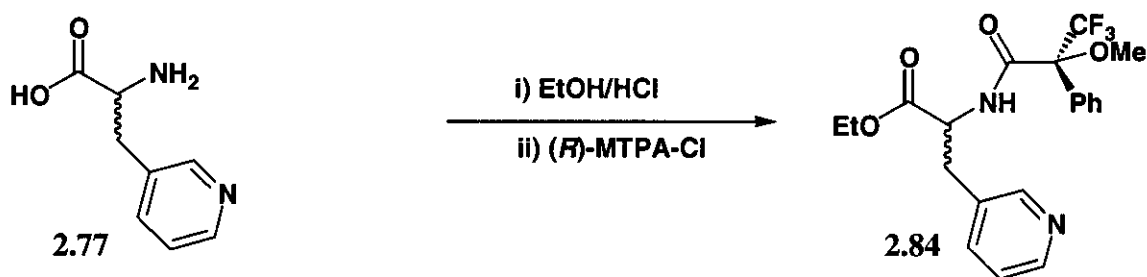
Prepared following the general method using **2.75** (~50 mg). δ_F -68.076 (minor diastereoisomer, 19.5%), -67.959 (major diastereoisomer, 80.5%); e.e. 61%.

(2'*S*)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(2-pyridyl)propanoate, 2.83



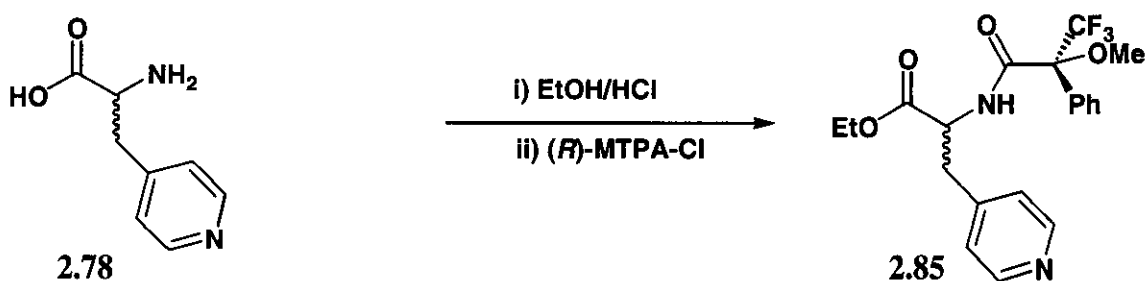
Prepared following the general method using **2.76** (~50 mg). δ_F -69.146 (major diastereoisomer, 55%), -69.518 (minor diastereoisomer, 45%); e.e. 10%.

(2'*S*)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(3-pyridyl)propanoate, 2.84



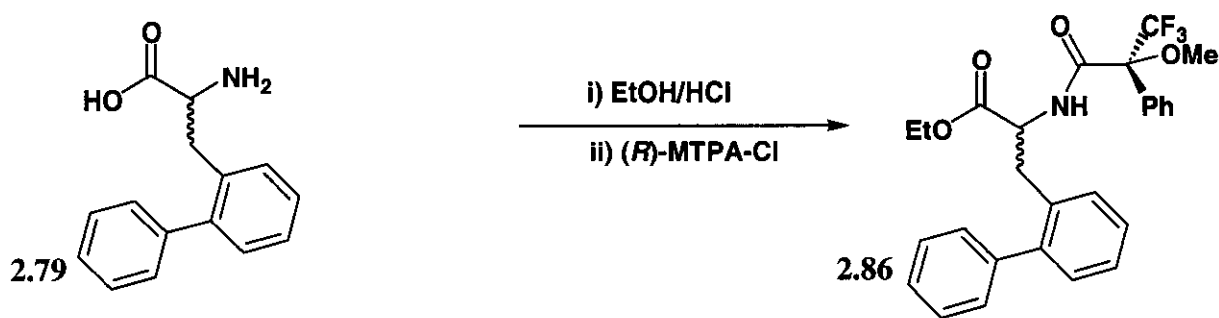
Prepared following the general method using **2.77** (~50 mg). δ_F -68.851 (minor diastereoisomer, 13%), -69.166 (major diastereoisomer, 87%); e.e. 74%.

(2'*S*)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(4-pyridyl)propanoate, 2.85



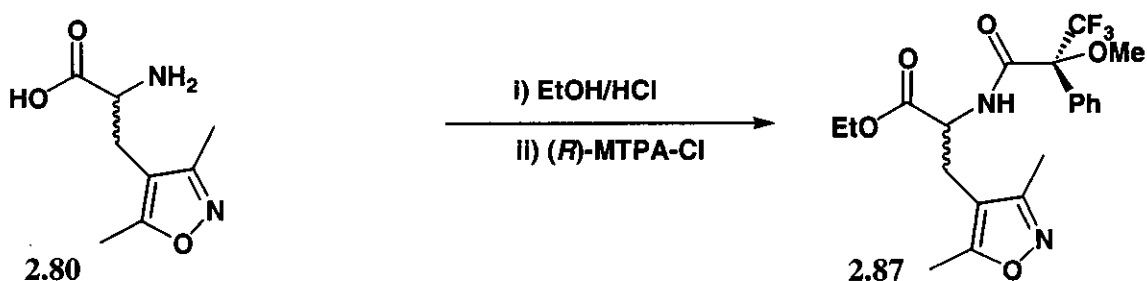
Prepared following the general method using **2.78** (~50 mg). δ_F -68.947 (minor diastereoisomer, 16%), -69.146 (major diastereoisomer, 84%); e.e. 68%.

(2'S)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(2-phenylphenyl)propanoate, 2.86



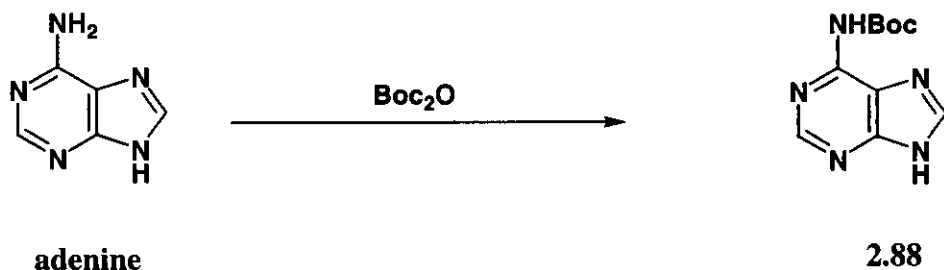
Prepared following the general method, using **2.79** (~50 mg). δ_F -68.011 (major diastereoisomer, 87%), -68.125 (minor diastereoisomer, 13%); e.e. 74%.

(2'S)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(3,5-dimethylisoxazol-4-yl)propanoate, 2.87



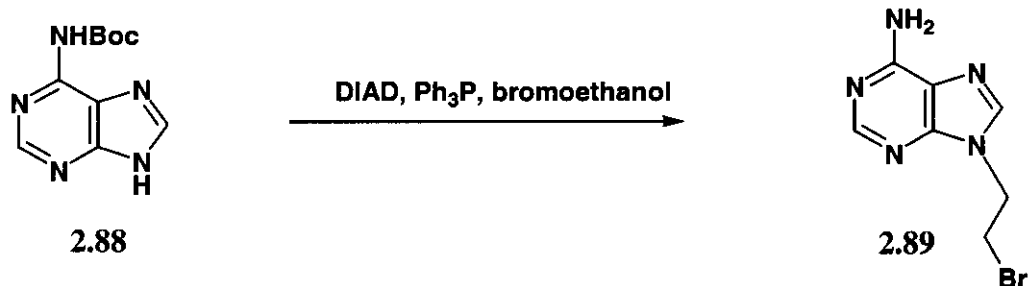
Prepared following the general method, using **2.80** (~50 mg). δ_F -68.869 (major diastereoisomer, 87%), -69.003 (minor diastereoisomer, 13%); e.e. 74%.

N6-Boc-Adenine, 2.88



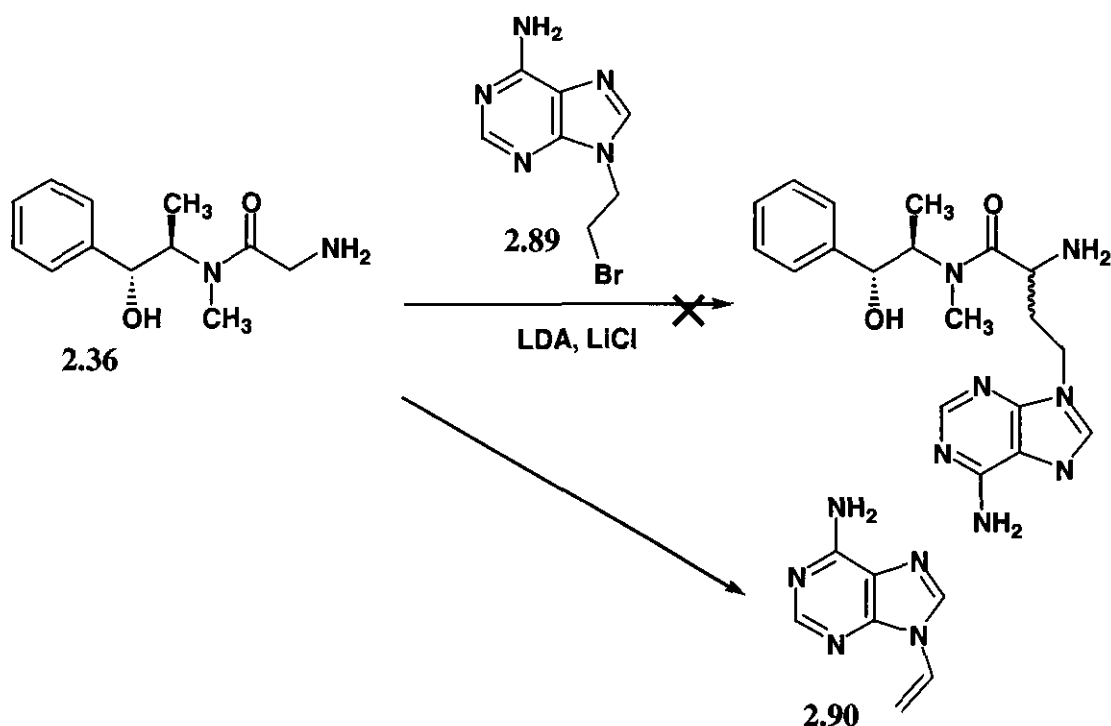
Adenine (5g, 37.0 mmol) and triethylamine (4.12g, 41 mmol) were vigorously stirred in DCM (100ml). After 30 min, di-*tert*-butyldicarbonate (9.8g, 41 mmol) in dichloromethane (20 ml) was added dropwise to the reaction mixture. The mixture was then heated at reflux overnight. The reaction was cooled to room temperature and concentrated in *vacuo* to give a white solid which was purified by column chromatography (DCM:MeOH, 73:7, v/v) to yield the title compound (6.52g, 75%) as white solid. M.p.>250°C; δ_{H} 1.6 (9H, s, CMe_3), 8.2 (1H, s, 2-H), 8.4 (1H, s, 8-H); δ_{C} 27.9 (CMe_3), 86.7 (CMe_3), 120.0 (CH), 139.4 (CH), 149.8, 155.0 and 155.7 (3 \times adenine quaternary C), 165.0 (C=O).

***N*9-(2-Bromoethyl)adenine, 2.89**



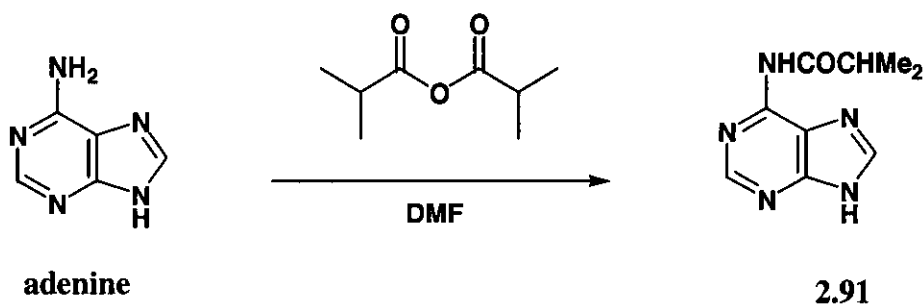
DIAD (5.16g, 25.5mmol) in dioxane (20ml) was added dropwise to a suspension of *N*6-Boc-adenine (5.0g, 21.3mmol), 2-bromoethanol (3.19g, 25.5mmol) and triphenylphosphine (6.69g, 25.5mmol) in dioxane (100ml) at 0°C. The mixture was stirred overnight to give a cloudy yellow solution. The solvent was removed and the yellow residue purified by column chromatography (DCM:MeOH, 10:0.5, v/v) to yield the title compound (2.51g, 21%) as a white crystalline solid. M.p.192-193°C (lit.¹⁰⁷ 195-197°C); δ_{H} (CD_3OD) 3.8 and 4.6 (each 2H, t, J 5.9, CH_2CH_2), 8.05 and 8.1 (each 1H, s, adenine H); δ_{C} 30.9 and 46.6 (CH_2CH_2), 120 and 143 (CH), 143.0, 150.6 and 153.7 (quaternary C); m/z 243 (EI) ($\text{M}^+ ^{81}\text{Br}$, 10%), 109 (40).

Attempted synthesis of (1*R*, 2*R*, 2*S'*)-2'-Amino-4'-(*N*9-adeninyl)butanoylpseudoephedrine, 2.90



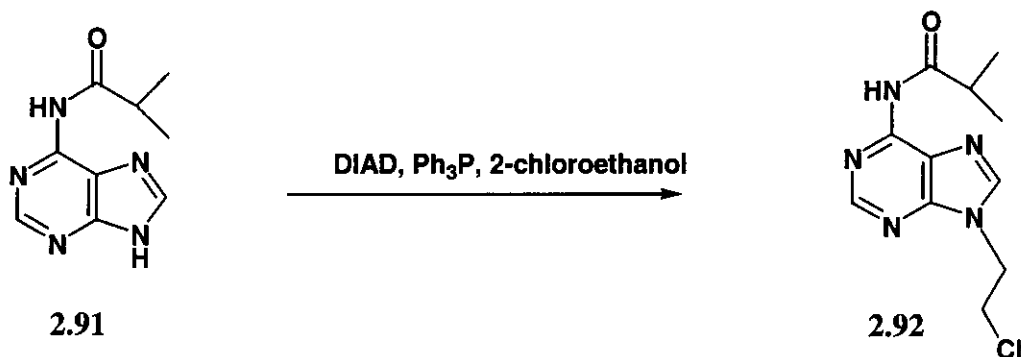
This was attempted following the general method using (1*R*,2*R*)-pseudoephedrine glycineamide (0.58 g, 2.61 mmol), lithium chloride (0.67 g, 15.8 mmol), LDA (2.58 ml, 5.16 mmol) and *N*9-(2-bromoethyl)adenine (0.7 g, 2.89 mmol). Work-up of the reaction mixture in the usual manner afforded *N*9-ethenyladenine¹⁰⁷ as a white solid (0.36 g, 77%). M.p. 200-201°C (lit.¹⁰⁷ 201-203°C); δ_{H} (CD₃OD) 5.2 (1H, dd, *J* 7.6 and 1.5, CH=CH₂), 6.0 (1H, dd, *J* 16.0 and 1.5, CH=CH₂), 7.25 (2 (1H, dd, *J* 16.0 and 7.6, CH=CH₂), 8.2 (1H, s, adenine CH), 8.4 (1H, s, adenine CH).

***N*6-(2-Methylpropanoyl)adenine 2.91⁷⁷**



Adenine (10 g, 74 mmol) was stirred with 2-methylpropanoic anhydride (36.8 cm³, 35.1 g, 222 mmol) in DMF at 160°C for 6 h. After evaporation of the solvent, the residue was taken up in EtOH–H₂O (200 cm³, 1:1 v/v) and the mixture heated under reflux for 1 h. The solvents were evaporated under reduced pressure and the residue subjected to column chromatography (DCM:MeOH, 9:1 v/v) to afford the title compound **3.40** as a white solid (10.8 g, 71%), m.p. 223–224°C; δ_{H} (300MHz; DMSO-*d*₆) 1.20 (6H, d, *J* 6.8 Hz, CHMe₂), 2.97 (1H, septet, *J* 6.8 Hz, CHMe₂), 8.48 and 8.69 (each 1H, s, 2-CH and 8-CH), 11.2 and 12.3 (NHCO and NH) ; δ_{C} (75 MHz; DMSO-*d*₆) 19.2 (CH₃), 34.2 (CHMe₂), 113.85 and 144.5 (ArC), 145.7 and 151.2 (C-2 and C-8), 161.3 (ArC) and 177.2 (CO).

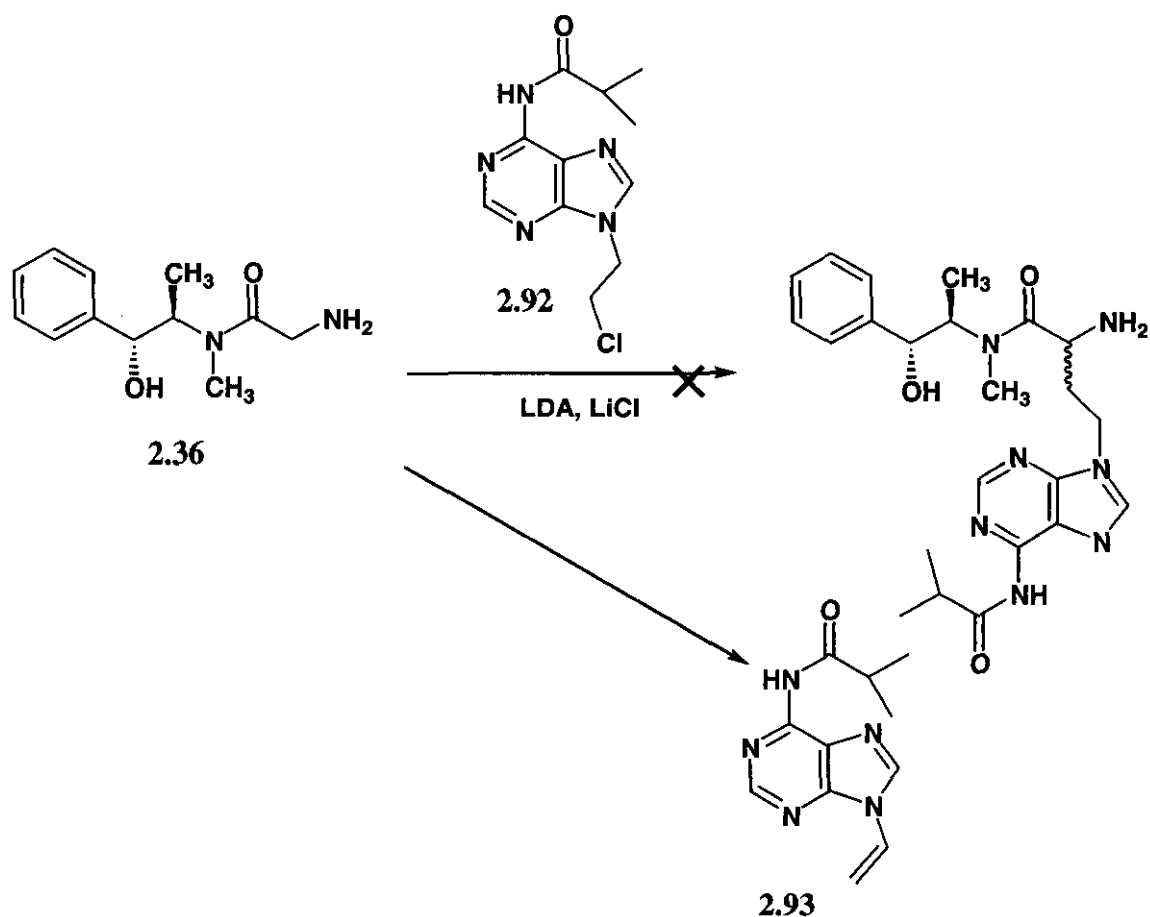
***N*9-(2-Chloroethyl)-*N*6-(2-methylpropanoyl)aminopurine, 2.92⁷⁷**



DIAD (2.53g, 12.5mmol) in dioxane (10ml) was added dropwise to a suspension of *N*6-(2-methylpropanoyl)aminopurine (2.14g, 10.4mmol), 2-chloroethanol (1.0g, 12.4mmol) and triphenylphosphine (3.29g, 12.5mmol) in 50ml of dry dioxane at 0°C under nitrogen. The mixture was stirred at room temperature overnight to yield a clear pale yellow

solution. The solvent was removed and the residue purified by recrystallisation from ethanol to give the title compound as white solid (1.98g, 71%). M.p. (decomp.) 160-162°C; Found: M^+ (EI) 267.0886; $C_{11}H_{14}ClN_5O$ requires: M^+ 267.0887. $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3246, 2972, 1686, 1602, 1576, 1520, 1338, 1228, 1195, 955; δ_{H} 1.26 (6H, d, J 5.1, CHMe_2), 3.28 (1H, septet, J 5.1, CHMe_2), 3.91 and 4.57 (each 2H, t, J 4.2, CH_2CH_2), 8.13 and 8.66 (each 1H, s, 2-CH and 8-CH), 9.19 (1H, s, CONH); δ_{C} 19.25 (CH_3), 35.95 (CHMe_2), 42.27 (CH_2Cl), 45.87 (NCH_2), 122.57 and 143.45 (quaternary C), 149.56 and 151.47 (C-2 and C-8), 152.56 (quaternary C) and 176.75 (CO); m/z 267 (EI) (M^+ , 22%), 197 (30) and 135 (100).

Attempted synthesis of (1*R*, 2*R*, 2*S'*)-2'-Amino-4'-[N6-(2-methylpropanoyl)-N9-adeninyl]butanoylpseudoephedrine, 2.93

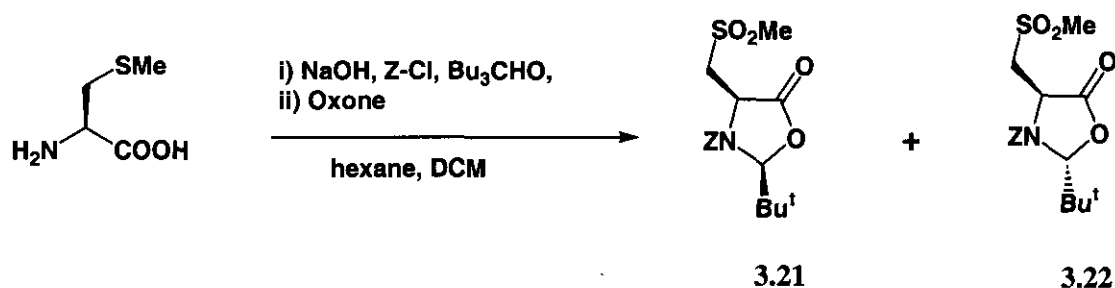


This was attempted following the general method using (1*R*,2*R*)-pseudoephedrine glycineamide (0.58 g, 2.61 mmol), lithium chloride (0.67 g, 15.8 mmol), LDA (2.58 ml, 5.16 mmol) and N6-(2-methylpropanoyl)-N9-(2-chloroethyl)adenine (0.7 g, 2.89 mmol).

Work-up in the usual manner afforded *N*6-(2-methylpropanoyl)-*N*9-vinyladenine (0.36 g, 77%) as part of an inseparable mixture with *N*6-(2-methylpropanoyl)-*N*9-(2-chloroethyl)adenine. Found: MH^+ (ES^+) 232.1201. $\text{C}_{11}\text{H}_{13}\text{N}_5\text{O}$ requires: MH 232.1120; δ_{H} 1.26 (6H, d, J 5.1, CHMe_2), 3.28 (1H, septet, J 5.1, CHMe_2), 5.20 (1H, d, J 8.8, $\text{CH}=\text{CH}_2$), 5.90 (1H, d, J 12.0, $\text{CH}=\text{CH}_2$), 7.19 and 7.25 (1H, $2 \times$ d, J 8.8 and 12.0, $\text{CH}=\text{CH}_2$), 8.24 and 8.71 (each 1H, s, 2-CH and 8-CH), 9.26 (1H, s, CONH); δ_{C} 19.25 (CH_3), 35.95 (CHMe_2), 105.24($\text{CH}=\text{CH}_2$), 122.19 (quaternary C), 126.27 ($\text{CH}=\text{CH}_2$), 140.23 (quaternary C), 149.62 and 150.82 (C-2 and C-8), 153.06 (quaternary C), 176.75 (C=O). m/z (EI) 231 (M^+ , 50%), 161 (70) and 134 (100).

Experimental 2 Radical approach

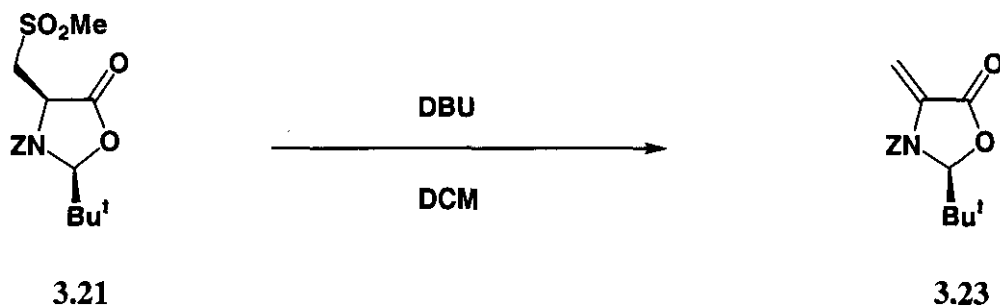
(2*S*,4*R*)-3-Benzoyloxycarbonyl-2-*tert*-butyl-4-(methylsulfonylmethyl)oxazolidin-5-one, 3.21, and the (2*R*,4*R*)-isomer, 3.22



(*R*)-*S*-Methylcysteine (27 g, 0.2 mol) was treated with aqueous sodium hydroxide (8.0 g, 0.2 mol, in 130 cm³ water), and after 5 min the solution was evaporated to dryness under reduced pressure to leave a white solid. A solution of pivaldehyde (21.7 cm³, 17.2 g, 0.2 mol) in hexane (300 cm³) was added and the suspension stirred and heated under reflux with Dean-Stark water removal for 24 h. The reaction mixture was then evaporated to dryness under reduced pressure and the white solid suspended in dry dichloromethane (250 cm³). Benzyl chloroformate (42.8 cm³, 51.1 g, 0.3 mol) was added dropwise to the stirred suspension at 0°C over 3 h. After stirring the mixture at room temperature for a further 36 h, aqueous sodium hydrogen carbonate (10% w/v, 100 cm³) was added and rapid stirring was continued for 4 h. The layers were then separated and the dichloromethane solution was dried (MgSO₄), filtered and evaporated. The residue was dissolved in acetonitrile (200 cm³) and oxone® (95 g, 0.15 mol) in water (500 cm³) was added. After 24 h at room temperature, water (200 cm³) was added, the mixture extracted with dichloromethane (3 x 200 cm³), and the combined extracts dried (MgSO₄), filtered and evaporated. Careful purification by column chromatography-(hexane:ethyl acetate, 9:1 to 3:1 v/v) gave the *title compounds* (42 g, 57% overall yield); *syn*-diastereoisomer **3.21** as an oil that gave white crystals from hexane, m.p. 151-152°C (38.19 g, 52%), and the *anti*-diastereoisomer **3.22** as a clear oil (3.80 g, 5%). (2*S*,4*R*)-3-Benzoyloxycarbonyl-2-*tert*-butyl-4-(methylsulfonylmethyl)oxazolidin-5-one **3.21** (*syn* diastereoisomer): [α]_D²² +27.0 (*c*, 2.00 in EtOH); Found: MH⁺ 370.1323. C₁₇H₂₃NO₆S requires: MH 370.1324; ν_{max}(film/cm⁻¹) 3056, 2980, 2877, 1796, 1729, 1635, 1397, 1316, 1266, 1131 and 1041; δ_H 0.95 (9H, s,

*CMe*₃), 3.11 (3H, s, SO₂Me), 3.41 (1H, dd, *J* 3.8, 15.2, CHHSO₂Me), 3.59 (1H, dd, *J* 8.0, 15.2, CHHSO₂Me), 4.99 (1H, dd, *J* 3.8, 8.0, CHCH₂), 5.18-5.27 (2H, 2 x d, *J* 11.9, CH₂Ph), 5.62 (1H, s, CHCMe₃) and 7.33-7.43 (5H, m, ArH); δ_C 24.6 (*CMe*₃), 37.2 (*CMe*₃), 42.5 (SO₂Me), 53.5 (CHCH₂), 57.2 (CH₂SO₂Me), 68.9 (CH₂Ph), 96.8 (CHO), 128.7, 128.8 and 128.8 (ArCH), 134.8 (ArC), 155.3 and 170.65 (CO). (2*R*,4*R*)-3-Benzoyloxycarbonyl-2-*tert*-butyl-4-(methylsulfonylmethyl)oxazolidin-5-one **3.22** (*anti*-diastereoisomer): [α]_D²² +72.8 (*c*, 0.32 in EtOH); Found: MH⁺ 370.1319. C₁₇H₂₃NO₆S requires: MH 370.1324; ν_{max}(film/cm⁻¹) 3056, 2973, 2877, 1797, 1713, 1639, 1413, 1354, 1317, 1266, 1127, 1035, 1015 and 975; δ_H 0.94 (9H, s, *CMe*₃), 2.91 (3H, s, SO₂Me), 3.57 (2H, d, *J* 14.1, CH₂SO₂Me), 4.45 (1H, br s, CHCH₂), 5.12-5.29 (2H, 2 x d, *J* 11.9, CH₂Ph), 5.68 (1H, s, CHCMe₃) and 7.23-7.47 (5H, m, ArH); δ_C 24.7 (*CMe*₃), 39.3 (*CMe*₃), 43.7 (SO₂CH₃), 53.6 (CHCH₂), 61.2 (CH₂SO₂Me), 68.3 (CH₂Ph), 96.0 (CHO), 128.7, 128.7 and 129.0 (ArCH), 134.9 (ArC), 152.9 and 170.4 (CO).

(2*S*)-3-Benzoyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one 3.23

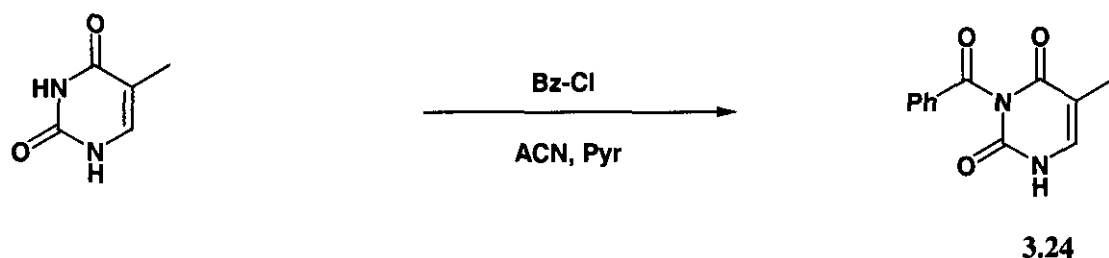


(2*S*,4*R*)-3-Benzoyloxycarbonyl-2-*tert*-butyl-4-(methylsulfonylmethyl)oxazolidin-5-one **3.21** (2.85 g, 7.72 mmol) in dry dichloromethane (40 cm³) was treated dropwise with DBU (1.39 cm³, 1.41 g, 9.27 mmol) and stirred at 0°C for 1 h before addition of water (40 cm³). The layers were separated and the dichloromethane solution was washed with water, dried (MgSO₄), filtered and evaporated under reduced pressure. The crude product was filtered through a short column of silica gel to give a colorless oil that crystallized from hexane to yield the *title compound* **3.23** (2.13 g, 95%) as a colorless crystalline solid, m.p. 69-71°C, [α]_D²⁰ -65.4 (*c*, 0.4 in EtOH); Found: MH⁺ 290.1394. C₁₆H₁₉NO₄ requires: MH 290.1392; ν_{max}(KBr/cm⁻¹) 3093, 3068, 3052, 1790, 1724, 1680, 1391, 1369, 1329, 1272, 1257, 1162, 1133, 1095, 1036 and 1012; δ_H 0.93 (9H, s, *CMe*₃), 5.27 (2H, s, CH₂Ph), 5.63 (2H, s,

C=CH₂), 5.71 (1H, s, CHCMe₃), 7.26-7.39 (5H, m, ArH); δ_c 24.3 (CMe₃), 38.6 (CMe₃), 68.7 (CH₂Ph), 93.9 (CHCMe₃), 104.2 (C=CH₂), 128.65, 128.7 and 128.81 (ArCH), 130.2 and 134.7 (2 \times quaternary C), 152.3 and 164.5 (C=O).

N3-Benzoylthymine 3.24 and **N3-benzoyluracil 3.29** were prepared by the method of Reese *et al.*⁹³ **N6-(2-Methylpanoyl)adenine 2.91**⁷⁷ and **N2-acetyl-O6-[2-(4-nitrophenyl)ethyl]guanine 3.44**¹⁰⁰ were prepared according to the methods of Shevlin *et al.*

N3-Benzoylthymine 3.24⁹³



Benzoyl chloride (2.55 cm³, 3.09 g, 22 mmol) was added dropwise at room temperature to a stirred suspension of powdered thymine (1.26 g, 10 mmol) in acetonitrile (10 cm³) and pyridine (4 cm³). The mixture was then stirred at room temperature overnight before the solvents were removed under reduced pressure. The residue was treated with potassium carbonate in dioxane–water (0.25M, 20 cm³, 1:1 v/v) for 2 h. The solution was then filtered, washed with acetonitrile (10 cm³) and dried under vacuum for 24 h to afford the title compound **3.24** as a white solid (1.54 g, 67%), m.p. 168-170°C (lit.⁹³ 150-152°C); Found: M⁺ 231.0769. C₁₂H₁₀N₂O₃ requires: M 231.0766; ν_{\max} (KBr/cm⁻¹) 3119, 1754, 1746, 1694, 1650, 1434, 1364 and 1193; δ_H (300MHz; DMSO-*d*₆) 1.81 (3H, s, CH₃), 7.52 (3H, m, ArH), 7.76 (1H, m, ArH), 7.93 (2H, m, ArH) and 11.36 (1H, d, *J* 5.3 Hz, NH); δ_c (75 MHz; DMSO-*d*₆) 11.7 (CH₃), 107.9 (C-5), 129.3, 129.5, 130.2 and 135.3 (C-6 and ArCH), 138.8 (ArC), 163.6, 167.3 and 170.1 (CO); *m/z* 231 (M⁺, 25%), 146 (53), 105 (100), 77 (70) and 51 (34).

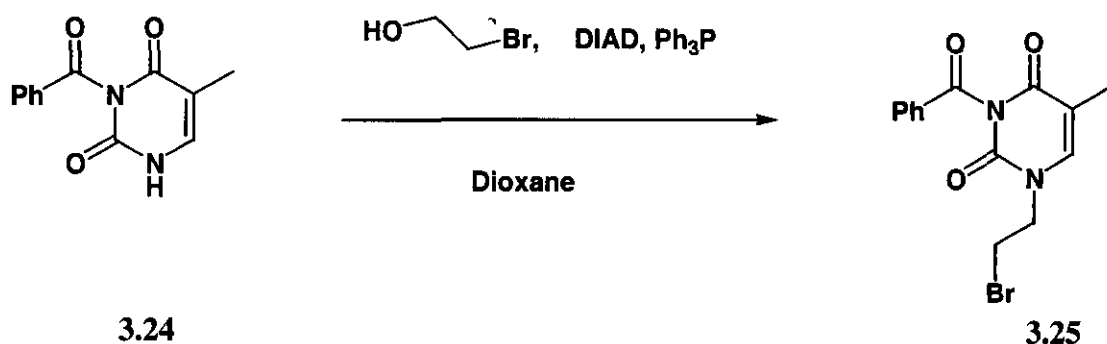
General procedure for the Mitsunobu reaction in the preparation of *N*-(ω -bromoalkyl) nucleobase derivatives (method A)

To a suspension of a suitably protected nucleobase (1 mol equiv.), triphenylphosphine (1.2 mol equiv.) and the ω -bromoalcohol (1.2 mol equiv.) in dry dioxane at 0°C was added DIAD (1.2 mol equiv.) dropwise over 3 h. The mixture was then stirred under argon at room temperature overnight to yield a clear solution. The solvent was removed and the residue purified by column chromatography to give the *N*-(ω -bromoalkyl) nucleobase derivative.

General procedure for conversion of the *N*-(ω -bromoalkyl) nucleobase derivatives into *N*-(ω -iodoalkyl) derivatives (method B)

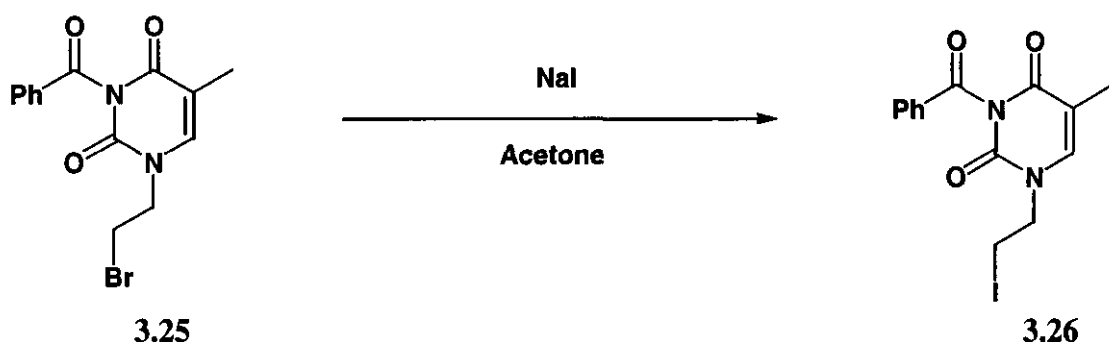
The *N*-(ω -bromoalkyl) nucleobase derivative (1 mol equiv.) and dry sodium iodide (5 mol equiv.) were heated in dry acetone (100 cm³) at reflux under argon overnight in the dark (aluminium foil). After cooling, the acetone was removed under reduced pressure and the residue taken up in ethyl acetate (100 cm³) and water (100 cm³). The organic layer was separated and washed with aqueous sodium thiosulfate solution (2% w/v, 2 x 50 cm³). The solution was dried (MgSO₄) and the solvent removed under reduced pressure to yield the *N*-(ω -iodoalkyl) derivative.

*N*3-Benzoyl-*N*1-(2-bromoethyl)thymine, 3.25



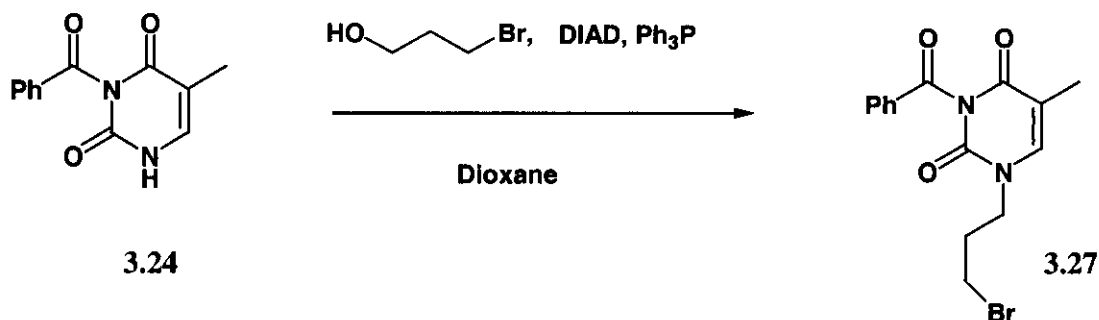
Prepared following method A, using *N*3-benzoylthymine **3.24** (4.0 g, 17.4 mmol), triphenylphosphine (5.47 g, 20.9 mmol), 2-bromoethanol (1.48 cm³, 2.61 g, 20.9 mmol), dioxane (150 cm³) and DIAD (4.11 cm³, 4.22 g, 20.9 mmol). Purification by column chromatography (hexane:ethyl acetate 6:4 v/v) gave the *title compound* **3.25** as a white amorphous solid (5.22 g, 89%), m.p. 183-184°C; Found: MNH₄⁺ (⁷⁹Br; CI) 354.0453. C₁₄H₁₃⁷⁹BrN₂O₃ requires: MNH₄ 354.0455; ν_{\max} (KBr/cm⁻¹) 2926, 2854, 2723, 1752, 1700, 1659, 1441, 1378 and 1360; δ_{H} 1.95 (3H, d, *J* 1.1, CH₃), 3.64 and 4.09 (each 2H, t, *J* 5.9, CH₂CH₂), 7.18 (1H, q, *J* 1.1, CH=CCH₃), 7.50 (2H, m, ArH), 7.65 (1H, m, ArH) and 7.92 (2H, m, ArH); δ_{C} 12.35 (CH₃), 29.3 and 50.7 (CH₂), 110.3 (C-5), 129.2, 130.4, 131.4 and 135.2 (ArCH and C-6), 140.9 (ArC), 149.6, 163.1 and 168.8 (CO); *m/z* (EI) 339.1 (MH; ⁸¹Br, 100%), 337.1 (MH; ⁷⁹Br, 96), 310.1 (93), 308.1 (100), 268.1 (28), 266 (31).

*N*3-Benzoyl-*N*1-(2-iodoethyl)thymine **3.26**



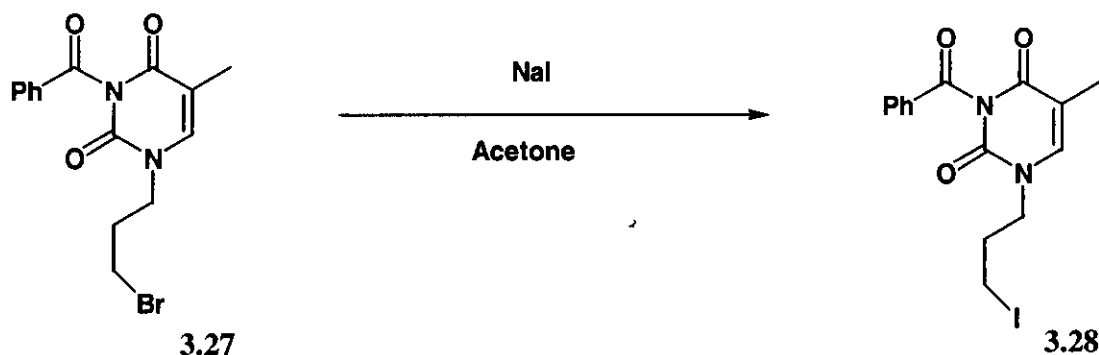
Prepared following method B, using *N*3-benzoyl-*N*1-(2-bromoethyl)thymine **3.25** (4.0 g, 11.4 mmol) and sodium iodide (8.56 g, 57.1 mmol) to yield the *title compound* **3.26** as a yellow powder (4.32 g, 95%), m.p. 138-139°C. Found: MH⁺ 385.0049. C₁₄H₁₃IN₂O₃ requires: MH 385.0053; ν_{\max} (KBr/cm⁻¹) 3119, 1754, 1746, 1694, 1650, 1434, 1364 and 1193; δ_{H} 1.95 (3H, s, CH₃), 3.4 and 4.07 (each 2H, t, *J* 6.2, CH₂CH₂), 7.14 (1H, s, CH=CCH₃), 7.52 (2H, m, ArH), 7.66 (1H, m, ArH) and 7.93 (2H, m, ArH); δ_{C} 12.35 (CH₃), 41.85 and 50.85 (CH₂), 110.4 (C-5), 129.2, 130.4, 131.4 and 135.1 (ArCH and C-6), 141.1 (ArC), 149.7, 163.1 and 168.7 (CO); *m/z* 385 (MH⁺, 62%), 356 (100), 314 (18), 229 (20) and 202 (60).

***N*3-Benzoyl-*N*1-(3-bromopropyl)thymine, 3.27**



Prepared following method A, using *N*3-benzoylthymine **3.24** (3.0 g, 13.0 mmol), triphenylphosphine (4.11 g, 15.7 mmol), 3-bromo-1-propanol (1.42 cm³, 2.18 g, 15.7 mmol) in dry dioxane (150 cm³) and DIAD (3.08 cm³, 3.17 g, 15.7 mmol). Purification by column chromatography (hexane:ethyl acetate 1:1 v/v) gave the *title compound* **3.27** as a white solid (4.20 g, 92%), m.p. 89-90°C. Found: MH⁺ (CI) 351.0343. C₁₅H₁₅BrN₂O₃ requires MH 351.0344; ν_{\max} (KBr/cm⁻¹) 3079, 2966, 1753, 1698, 1664, 1648, 1597, 1463, 1348, 1257 and 1179; δ_{H} 1.97 (3H, d, *J* 0.9, CH₃), 2.28 (2H, apparent quintet, *J* 6.6, CH₂CH₂CH₂), 3.91 (2H, t, *J* 6.2, CH₂Br), 4.09 (2H, t, *J* 6.8, NCH₂), 7.18 (1H, q, *J* 1.0, CH=CCH₃), 7.50 (2H, m, ArH), 7.65 (1H, m, ArH) and 7.92 (2H, m, ArH); δ_{C} 12.35 (CH₃), 29.3, 31.0 and 50.7 (CH₂), 110.3 (C-5), 129.2, 130.4, 135.2 and 131.4 (ArCH and C-6), 140.9 (ArC), 149.6, 163.1 and 168.8 (CO). *m/z* 351 (M⁺, 10%), 322 (100), 282 (40), 243 (80), 229 (10) and 216 (25).

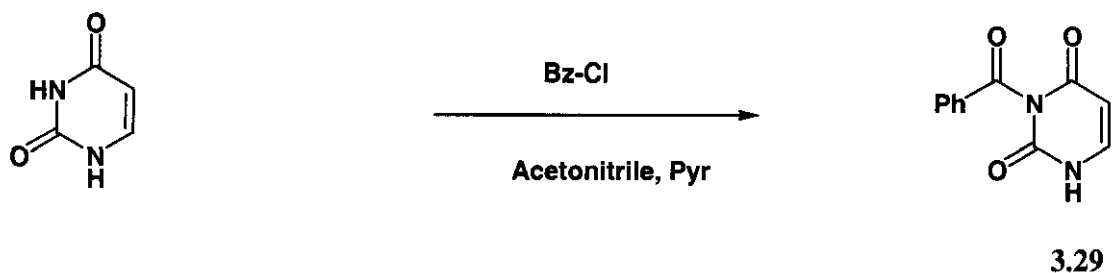
***N*3-Benzoyl-*N*1-(3-iodopropyl)thymine, 3.28**



Prepared following method B, using *N*3-benzoyl-*N*1-(3-bromopropyl)thymine **3.27** (4.0 g, 11.4 mmol) and sodium iodide (8.56 g, 57.1 mmol) to yield the *title compound* **3.28** as a

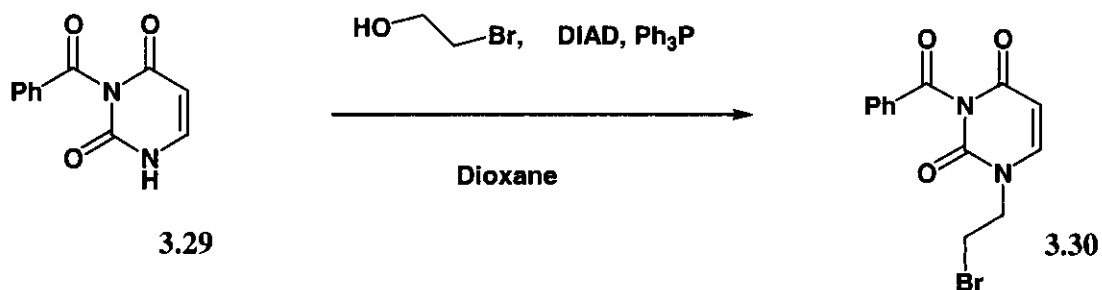
yellow powder (4.32 g, 95%), m.p. 91-92°C. Found: MH^+ 399.0213. $C_{15}H_{15}IN_2O_3$ requires 399.0205; ν_{max} (KBr/ cm^{-1}) 3479, 1746, 1651, 1600, 1439, 1353, 1239 and 1176; δ_H 1.97 (3H, s, CH_3), 2.25 (2H, quintet, J 7.9, CH_2CH_2I), 3.21 (2H, t, J 6.4, CH_2I), 3.82 (2H, t, J 6.8, NCH_2), 7.17 (1H, s, $CH=CCH_3$), 7.45 (2H, t, J 7.9, $ArCH$), 7.62 (1H, t, J 7.9, $ArCH$), 7.93 (2H, d, J 6.4, $ArCH$); δ_C 1.62 (CH_2I) 12.37 (CH_3), 31.82 and 49.48 (CH_2), 110.92 ($CH=CCH_3$), 129.12 and 130.38 and 131.51 ($ArCH$), 135.02 and 140.21 ($C-CH_3$ and ArC), 149.78, 163.02 and 168.90 ($C=O$); m/z M^+ 398 (15%), 370 (30), 328 (20), 277 (100), 243 (60) and 167 (18).

***N*3-Benzoyluracil 3.29⁹³**



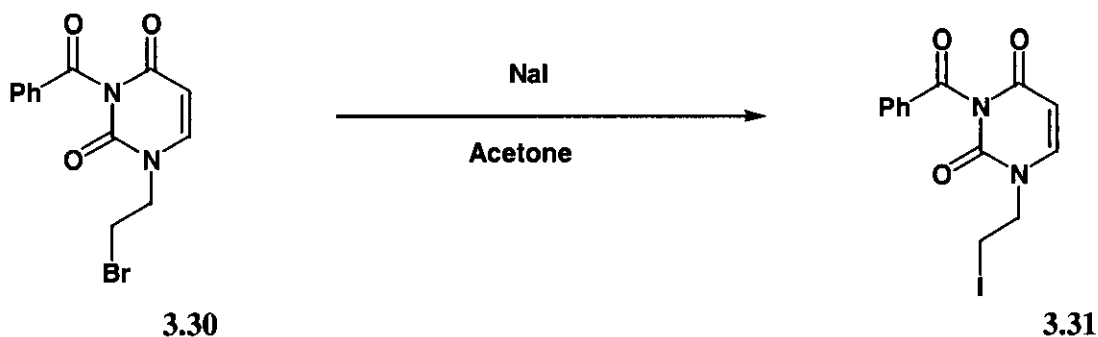
Prepared using the method described above for *N*3-benzoylthymine **3.24**, using benzoyl chloride (6.83 cm^3 , 8.28 g, 58.9 mmol), uracil (3.0 g, 26.8 mmol) in acetonitrile (50 cm^3) and pyridine (20 cm^3) and then potassium carbonate in dioxane–water (0.25M, 100 cm^3 , 1:1 v/v). Filtration, washing the solid with acetonitrile (20 cm^3) and drying under vacuum afforded the title compound **3.29** as a white solid (3.58 g, 62%), m.p. 168-170 °C (lit.⁹³ 148-149°C); Found: MH^+ 217.0613. $C_{11}H_8N_2O_3$ requires: MH 217.0613; δ_H (300 MHz; DMSO- d_6) 5.29 (1H, d, J 7.7 Hz, $CH=CHCO$), 7.14 (2H, t, J 7.9 Hz, $ArCH$), 7.20 (1H, d, J 7.9 Hz, $CH=CHCO$), 7.30 (1H, t, J 7.3, ArH), 7.53 (2H, d, J 7.2, ArH), 11.17 (1H, s, NH); δ_C (75 MHz; DMSO- d_6) 100.1 (C-5), 129.5, 130.3, 131.4 and 135.4 (C-6 and $ArCH$) 143.3 (ArC), 150.1, 163.0 and 170.1 (CO); m/z 217 (MH^+ , 15%), 139 (60), 130 (100), 122 (40), 113 (50) and 52 (48).

***N*3-Benzoyl-*N*1-(2-bromoethyl)uracil, 3.30**



Prepared following method A, using *N*3-benzoyluracil **3.29** (4.2 g, 19.4 mmol), triphenylphosphine (6.12 g, 23.3 mmol) and 2-bromoethanol (1.65 cm³, 2.92 g, 23.3 mmol) in dry dioxane (150 cm³) and DIAD (4.59 cm³, 4.72 g, 23.3 mmol). Purification by column chromatography (hexane:ethyl acetate 6:4 v/v) gave the *title compound* **3.30** as a white solid (5.15 g, 82%), m.p. 183-184°C. Found: (MNH₄⁺; ⁷⁹Br) (ES⁺) 340.0290. C₁₃H₁₁⁷⁹BrN₂O₃ requires: MNH₄ 340.0297; ν_{\max} (KBr/cm⁻¹) 3110, 1744, 1699, 1664, 1449, 1349 and 1258; δ_{H} 3.65 and 4.13 (each 2H, t, *J* 5.9, CH₂CH₂), 5.74 and 7.31 (each 1H, d, *J* 7.7, CH=CHCO), 7.48 (2H, m, ArH), 7.65 (1H, m, ArH), 7.93 (2H, m, ArH); δ_{C} 29.4 and 51.1 (CH₂), 101.8 (C-6), 129.25, 130.5, 131.3 and 135.3 (ArCH and C-5), 144.9 (ArC), 149.6, 162.3 and 168.45 (CO); *m/z* 324 (MH⁺, 100%).

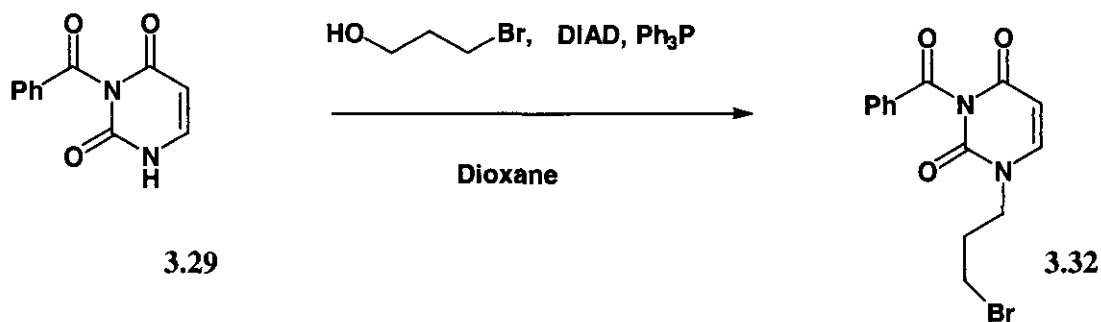
***N*3-Benzoyl-*N*1-(2-iodoethyl)uracil, 3.31**



Prepared following method B, using *N*3-benzoyl-*N*1-(2-bromoethyl)uracil **3.30** (5.0 g, 15.5 mmol) and sodium iodide (11.64 g, 77.6 mmol) to yield the *title compound* **3.31** as a yellow powder (5.52 g, 96%), m.p. 190-191°C. Found: MH⁺ (CI) 370.9892. C₁₃H₁₁IN₂O₃ requires: MH 370.9892; ν_{\max} (KBr/cm⁻¹) 3109, 1743, 1700, 1663, 1447, 1344 and 1178; δ_{H} 3.44 and 4.13 (each 2H, t, *J* 6.2, CH₂CH₂), 5.84 and 7.23 (each 1H, d, *J* 7.9, CH=CHCO), 7.49 (2H, m, ArH), 7.66 (1H, m, ArH) and 7.95 (2H, m, ArH); δ_{C} 21.9 and

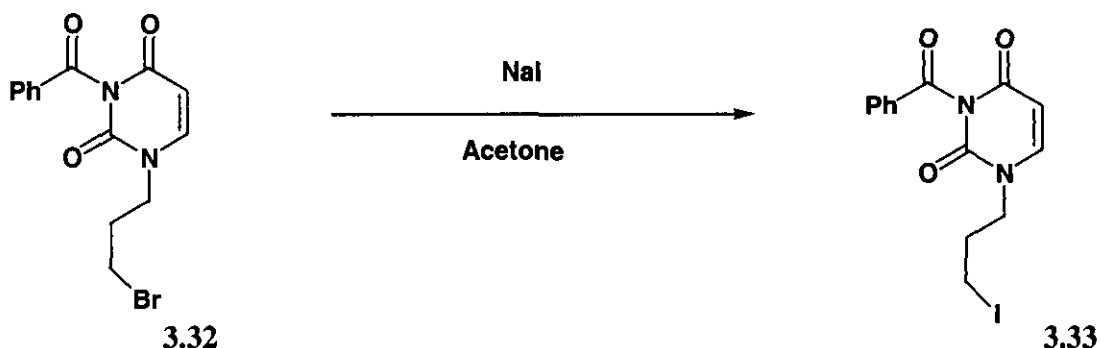
51.5 (CH₂), 101.9 (C-5), 129.25, 130.5, 131.3, 135.2 (ArCH and C-6), 144.3 (ArC), 149.5, 162.25 and 168.44 (CO); *m/z* 371 (MH⁺, 4%), 342 (100), 277 (30), 215 (40), 188 (60) and 155 (50).

***N*3-Benzoyl-*N*1-(3-bromopropyl)uracil, 3.32**



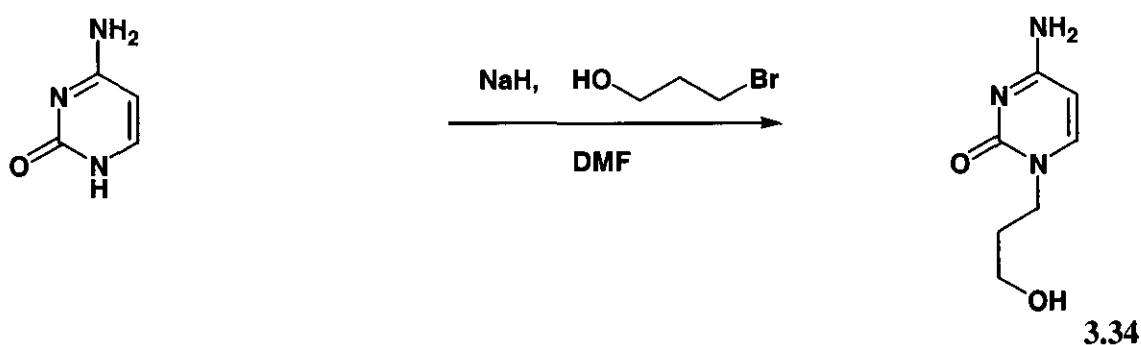
Prepared following method A, using *N*3-benzoyluracil **3.29** (3.5 g, 16.2 mmol), triphenylphosphine (5.10 g, 19.4 mmol) and 3-bromo-1-propanol (1.77 cm³, 2.70 g, 19.4 mmol) in dry dioxane (150 cm³) and DIAD (3.08 cm³, 3.83 g, 19.4 mmol). Purification by column chromatography (hexane:ethyl acetate, 1:1 v/v) gave the *title compound* **3.32** as a white solid (4.57 g, 84%), m.p. 89-90°C. Found: MH⁺ (CI) 337.0188. C₁₄H₁₃BrN₂O₃ requires: MH 337.0188; ν_{\max} (KBr/cm⁻¹) 1738, 1699, 1654, 1598, 1446, 1389, 1341 and 1256; δ_{H} 2.28 (2H, apparent quintet, *J* 6.4, CH₂CH₂CH₂), 3.44 (2H, t, *J* 6.1, CH₂Br), 3.94 (2H, t, *J* 6.6, NCH₂), 5.80 and 7.35 (each 1H, d, *J* 8.1, CH=CHCO), 7.51 (2H, m, ArH), 7.65 (1H, m, ArH) and 7.93 (2H, m, ArH); δ_{C} 29.7, 30.95 and 47.9 (CH₂), 102.2 (C-5), 129.2 and 130.45 (ArCH), 131.4 (ArC), 135.2 and 144.5 (ArCH and C-6), 149.8, 162.35 and 168.75 (CO); *m/z* 337 (MH⁺, 40%), 276 (30), 259 (40), 172 (100), 155 (46), 139 (44) and 105 (34).

***N*3-Benzoyl-*N*1-(3-iodopropyl)uracil, 3.33**



Prepared following method B, using *N*3-benzoyl-*N*1-(3-bromopropyl)uracil **3.32** (4.5 g, 13.4 mmol) and sodium iodide (10.0 g, 67.0 mmol) to yield the *title compound* **3.33** as a yellow gum (5.0 g, 96%); Found: MH^+ 385.0052. $C_{14}H_{13}IN_2O_3$ requires: MH 385.0049; $\nu_{max}(KBr/cm^{-1})$ 3056, 1751, 1708, 1669, 1440 and 1266; δ_H 2.21 (2H, apparent quintet, J 6.6, $CH_2CH_2CH_2$) 3.14 (2H, t, J 6.6, CH_2I), 3.82 (2H, t, J 6.8, NCH_2), 5.74 and 7.33 (each 1H, d, J 8.0, $CH=CHCO$), 7.49 (2H, m, ArH), 7.65 (1H, m, ArH) and 7.91 (2H, m, ArH); δ_C 1.53, 31.7 and 49.7 (CH_2), 102.0 (C-5), 129.2 and 130.3 (ArCH), 131.3 (ArC), 135.2 and 144.6 (ArCH and C-6), 149.7, 162.3 and 168.8 (CO); m/z 384 (M^+ , 8%), 356 (50), 328 (8), 314 (10), 263 (100) and 257 (65).

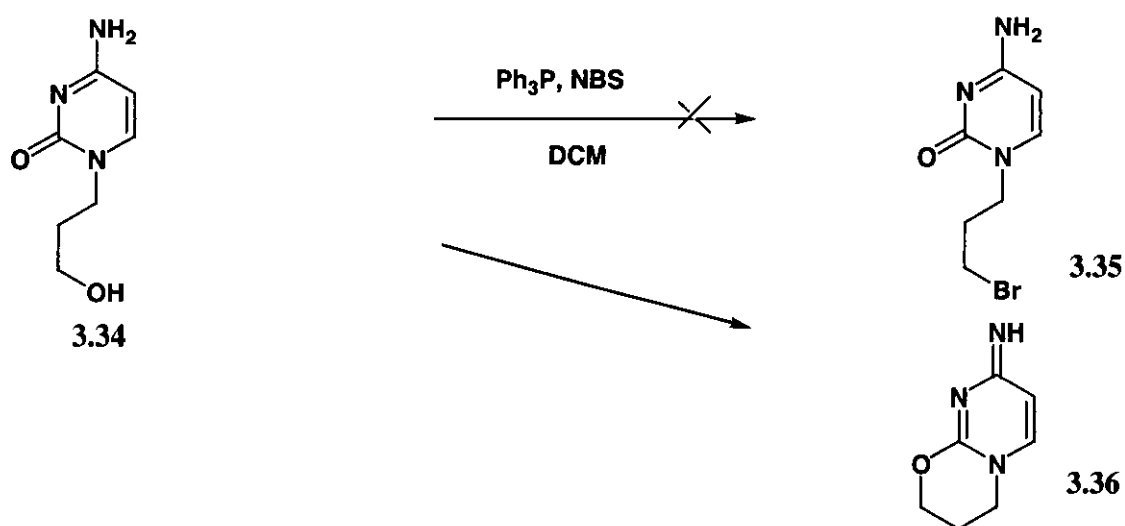
***N*1-(3-Hydroxypropyl)cytosine, 3.34**



This was prepared using a modified procedure of Keese⁹⁶. NaH (0.319 g, 13.3 mmol) was added portionwise to cytosine (1.48 g, 13.3 mmol) suspended in DMF (50 ml). After stirring at room temperature for 1 h, 3-bromo-1-propanol (1.20 ml, 1.85 g, 13.3 mmol) in DMF (5 ml) was added dropwise over 2 h (syringe pump) to the clear solution and the

mixture stirred for a further 16 h. Methanol was then added and the solvents were evaporated. The solid obtained was dissolved in methanol and silica gel was added. The mixture was dried and submitted to flash chromatography (DCM/MeOH/Et₃N, 93/5/2, v/v) to yield the *title compound* **3.34** as a white gum (1.46 g, 65%). Found (MH⁺) (ES+) 274.1194. C₁₄H₁₅N₃O₃ requires (MH) 274.1191; $\nu_{\max}(\text{KBr}/\text{cm}^{-1})$ 3420, 3170, 3100, 3040, 2930, 2850, 1705, 1640, 1500, 1435, 1380, 1260, 1235, 1160, 1070, 1015, 990; δ_{H} (DMSO-*d*₆) 1.76 (2 H, quintet, *J* 6.5, CH₂CH₂CH₂OH), 3.44 (2 H, t, *J* 6.1, CH₂OH), 3.74 (2 H, t, *J* 7.0, NCH₂), 4.61 (1H, broad s, CH₂OH), 5.71 (1 H, d, *J* 7.2, ArCH), 7.06 (2 H, broad s, NH₂), 7.59 (1 H, d, *J* 7.2, ArCH); δ_{C} 31.79 (CH₂CH₂CH₂), 46.01 (CH₂OH), 57.66 (NCH₂), 93.18 (ArCH), 146.23 (ArCH), 156.02 (ArC), 165.96 (C=O).

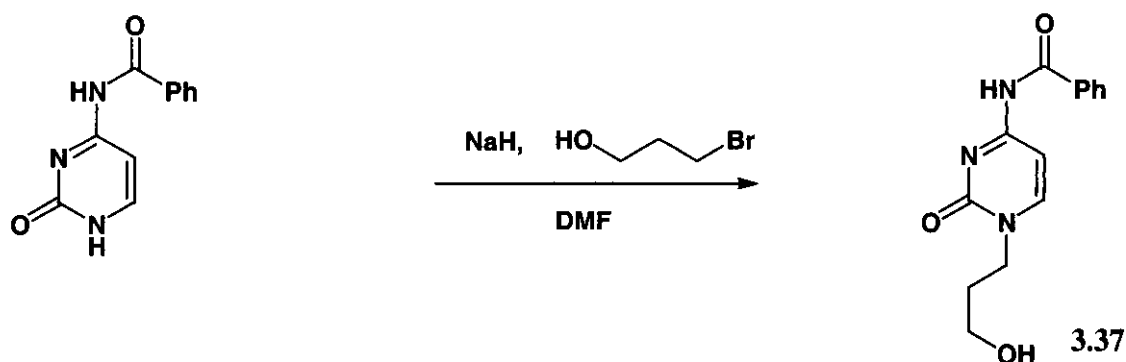
Attempted preparation of N1-(3-bromopropyl)cytosine, **3.35**



NBS (1.31 g, 7.36 mmol) was added portionwise to a stirred solution of 1-(3-hydroxypropyl)cytosine **3.34** (1.13 g, 6.69 mmol) and triphenylphosphine (1.93 g, 7.36 mol) in dichloromethane at -10°C (ice-salt bath). The mixture was stirred at -10°C for 3 h. The solvent was removed and the crude product purified by flash chromatography (DCM/MeOH/Et₃N, 93/5/2, v/v and 70/30, v/v MeOH/AcOH) to yield unreacted starting material (0.76 g, 67%) and the cyclised starting material **3.36** as a gum (0.21 g, 19%). δ_{H} (DMSO-*d*₆) 2.23 (2 H, quintet, *J* 5.3, CH₂CH₂CH₂O), 4.08 (2 H, t, *J* 5.9, CH₂), 4.57 (2

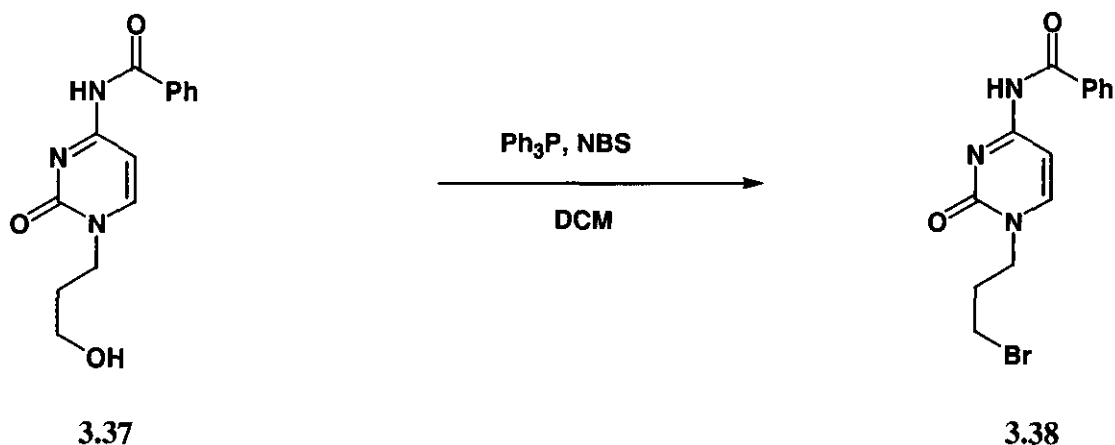
H, t, J 5.3, CH_2), 6.56 (1 H, d, J 7.1, ArCH), 7.94 (1 H, d, J 7.1, ArCH); δ_{c} 48.15 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 67.99 (CH_2O), 101.91 (NCH_2), 146.39 (ArCH), 155.67 (ArCH), 165.04 (ArC), 172.0 (C-O).

***N*4-Benzoyl-*N*1-(3-hydroxypropyl)-cytosine, 3.37**



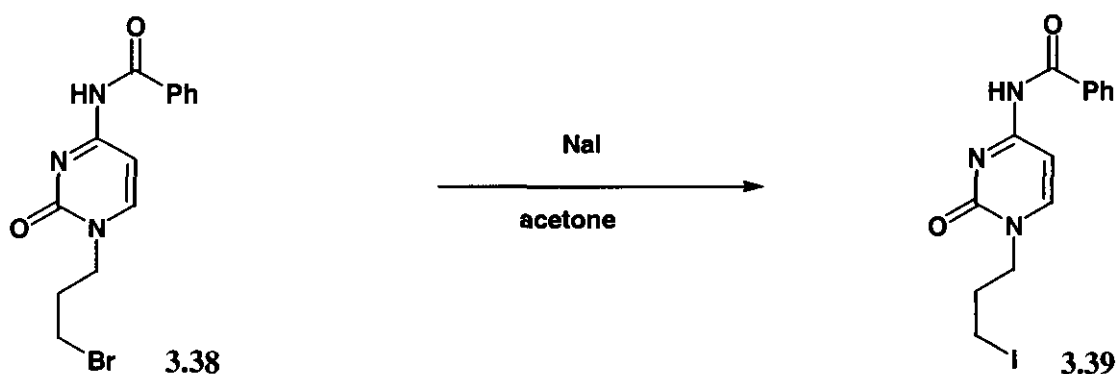
This was prepared using a modified procedure of Keese⁹⁶. NaH (0.310 g, 12.9 mmol) was added portionwise to *N*4-benzoylcytosine (2.78 g, 12.9 mmol) suspended in DMF (50 ml). After stirring at room temperature for 1 h, 3-bromo-1-propanol (1.17 ml, 1.80 g, 12.9 mmol) in DMF (5 ml) was added dropwise over 2 h (syringe pump) and the mixture stirred for a further 16 h. Methanol was then added and the solvents evaporated. The solid obtained was dissolved in methanol and silica gel was added. The mixture was dried and submitted to flash chromatography (DCM/MeOH, 95/5) to yield the *title compound* **3.37** as a white solid (2.14 g, 61%), m.p. 156-157°C; Found (MH^+) 274.1194 (ES^+) $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3$ requires (MH) 274.1191; ν_{max} ($\text{KBr}/\text{cm}^{-1}$) 3531, 3387, 3151, 3067, 2968, 1696, 1651, 1626, 1604, 1583, 1504, 1320, 1251, 1173, 1090, 796, 700; δ_{H} ($\text{DMSO}-d_6$) 1.84 (2 H, quintet, J 6.6, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.45 (2 H, q, J 5.1, CH_2OH), 3.92 (2 H, t, J 7.2, NCH_2), 4.65 (1 H, t, J 4.9, CH_2OH), 7.30 (1 H, d, J 7.2, ArCH), 7.52 (1 H, t, J 7.7, ArCH), 7.63 (2 H, t, J 7.3, ArCH), 8.03 (2 H, d, J 8.3, ArCH), 8.13 (1 H, d, J 7.3, ArCH), 11.18 (1 H, s, CONH); δ_{c} 31.16 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 47.19 (CH_2OH), 57.62 (NCH_2), 95.69, 128.32, 128.34 and 132.55 (ArCH), 133.21 (ArC), 150.33 (ArCH), 155.11 (C=O), 162.79 (ArC), 167.29 (C=O); m/z 273 (M^+ , 50%), 244 (60), 229 (90), 196 (100), 178 (30), 138 (70).

***N*4-Benzoylcytosine-*N*1-(3-bromopropyl)cytosine, 3.38**



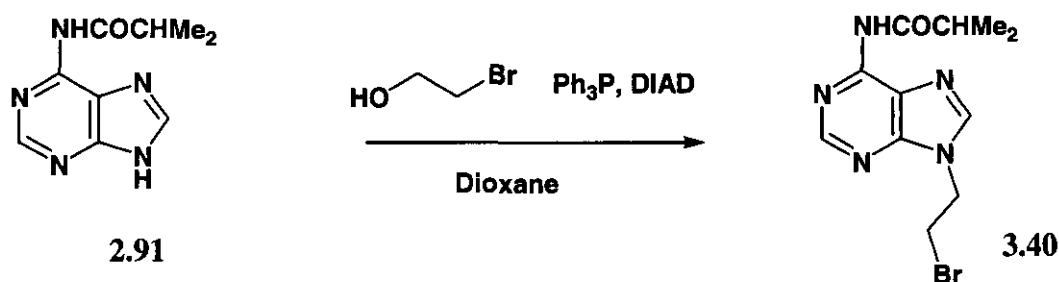
NBS (4.02 g, 22.6 mmol) was added portionwise to a stirred solution of *N*4-benzoyl-*N*1-(3-hydroxypropyl)cytosine **3.37** (5.60 g, 20.5 mmol) and triphenylphosphine (5.92 g, 22.6 mol) in dichloromethane at -10°C (ice-salt bath). The mixture was stirred at -10°C for 3 h. The solvent was removed and the crude product purified by flash chromatography (DCM/MeOH, 97/3, v/v) to yield *the title compound* **3.38** as a white amorphous solid (4.92g, 72%), m.p. $162\text{--}163^\circ\text{C}$; Found (MH^+) 336.0356 (ES^+) $\text{C}_{14}\text{H}_{14}^{79}\text{BrN}_3\text{O}_2$ requires (MH) 336.0347; ν_{max} ($\text{KBr}/\text{cm}^{-1}$) 3156, 3058, 3005, 1674, 1661, 1626, 1553, 1485, 1361, 1298, 1265, 809, 703; δ_{H} ($\text{DMSO}-d_6$) 2.24 (2 H, quintet, J 6.8, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.47 (2 H, t, J 6.6, CH_2Br), 3.95 (2 H, t, J 7.0, NCH_2), 7.31 (1 H, d, J 6.4, ArCH), 7.52 (1 H, t, J 7.7, ArCH), 7.63 (1 H, t, J 7.3, ArCH), 8.03 (2 H, d, J 8.3, ArCH), 8.13 (1 H, d, J 7.2, ArCH), 8.66 (1H, d, J 7.3, ArCH), 11.20 (1 H, s, CONH); δ_{C} 31.04 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 31.32 (CH_2Br), 48.57 (NCH_2), 95.87 (ArCH), 128.32, 128.77 and 132.07 (ArCH), 132.56 (ArC), 150.22 (ArCH), 155.32 (C=O), 162.85 (ArC), 167.34 (C=O); m/z 336 ($\text{M}+\text{H}$, 100%), 306 (90), 258 (90), 229 (90), 178 (60), 138 (90).

***N*4-Benzoyl-*N*1-(3-iodopropyl)cytosine, 3.39**



This was prepared following method B using *N*4-benzoyl-*N*1-(3-bromopropyl)cytosine **3.38** (3.04 g, 9.07 mmol) and dry sodium iodide (6.80 g, 45.4 mmol) to yield the *title compound* **3.39** as a yellow powder (3.14 g, 90%), m.p. 169-170°C. Found (MH⁺) 384.0216 (ES⁺) C₁₄H₁₄IN₃O₂ requires (MH) 384.0209 ; ν_{\max} (KBr/cm⁻¹) 3208, 3070, 1693, 1657, 1625, 1553, 1489, 1348, 1260, 803, 787, 699; δ_{H} (DMSO-*d*₆) 2.18 (2 H, quintet, *J* 7.0, CH₂CH₂CH₂), 3.25 (2 H, t, *J* 7.0, CH₂I), 3.89 (2 H, t, *J* 7.2, NCH₂), 7.31 (1 H, d, *J* 6.5, ArCH), 7.49 (1 H, t, *J* 7.7, ArCH), 7.61 (1 H, t, *J* 7.3, ArCH), 8.15 (2 H, d, *J* 8.0, ArCH), 8.13 (1 H, d, *J* 7.2, ArCH), 8.65 (1H, d, *J* 7.3, ArCH), 11.19 (1 H, s, CONH); δ_{C} - 19.03 (CH₂I), 49.74 (CH₂CH₂CH₂I), 69.24 (NCH₂), 105.06 (ArCH), 128.32, 128.53, 132.05 (ArCH), 133.45 (ArC), 151.88 (ArCH), 156.24 (ArC), 163.23, 167.53 (C=O); *m/z* 383 (M⁺, 40%), 354 (30), 306 (20), 256 (60), 226 (66), 178 (100), 122 (90), 151 (50).

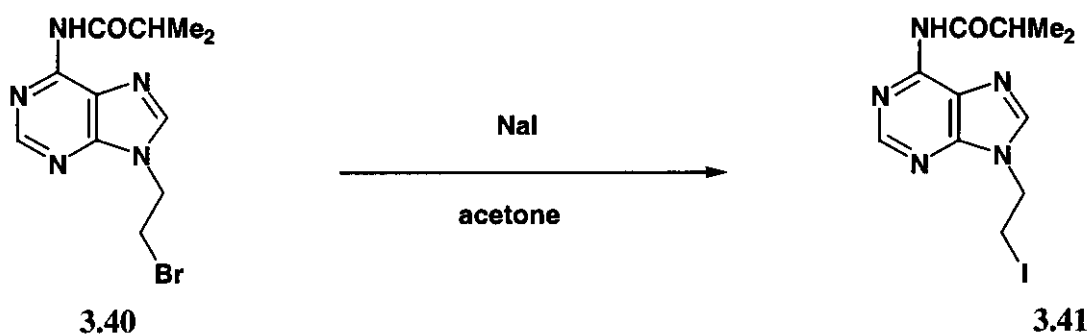
***N*9-(2-Bromoethyl)-*N*6-(2-methylpropanoyl)adenine, 3.40**



Prepared following method A, using *N*6-(2-methylpropanoyl)adenine **2.91** (5.0 g, 24.4 mmol), triphenylphosphine (7.68 g, 29.3 mmol) and 2-bromoethanol (2.07 cm³, 3.66 g,

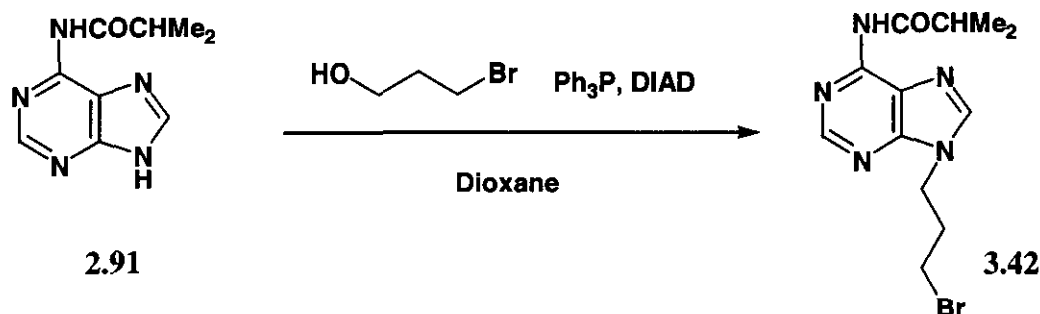
29.3 mmol), dioxane (150 cm³) and DIAD (5.76 cm³, 5.92 g, 29.3 mmol). Purification by column chromatography (hexane:ethyl acetate, 4:1 v/v) gave the *title compound* **3.40** as a white solid (5.76 g, 76%), m.p. 148-149°C (from ethanol); Found: MH⁺ 312.0462. C₁₁H₁₄BrN₅O requires: MH 312.0460; ν_{\max} (KBr/cm⁻¹) 3339, 3281, 3117, 2973, 1689, 1611, 1516, 1489, 1201 and 1152; δ_{H} 1.34 (6H, d, *J* 6.93, CHMe₂), 3.28 (1H, septet, *J* 6.9, CHMe₂), 3.79 and 4.69 (each 2H, t, *J* 5.9, CH₂CH₂), 8.12 and 8.70 (each 1H, s, 2-CH and 8-CH), 9.06 (1H, s, CONH); δ_{C} 19.4 (CH₃), 29.65 (CH₂Br), 36.0 (CHMe₂), 45.8 (NCH₂), 122.3 and 143.0 (ArC), 149.5 and 151.4 (C-2 and C-8), 152.6 (ArC) and 176.4 (CO); *m/z* 313 (M⁺, 100%), 311 (M⁺, 100%), 270 (12) and 268 (20).

***N*9-(2-Iodoethyl)-*N*6-(2-methylpropanoyl)adenine, 3.41**



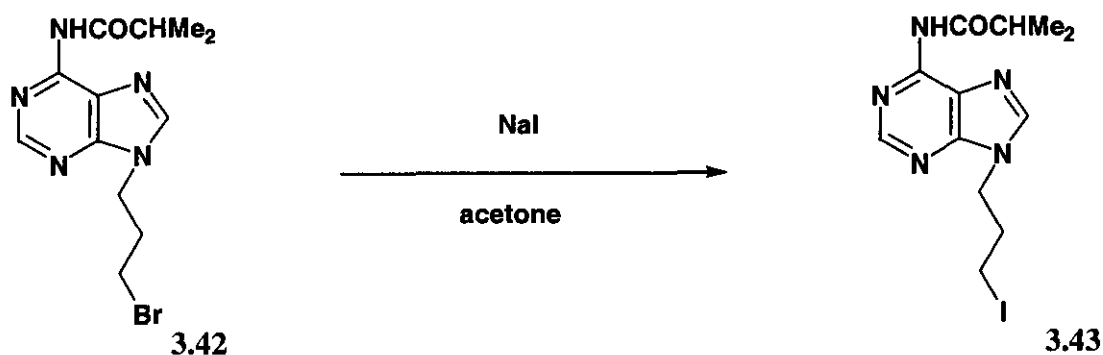
Prepared following method B, using *N*9-(2-bromoethyl)-*N*6-(2-methylpropanoyl)adenine **3.40** (5.0 g, 16.1 mmol) and sodium iodide (12.0 g, 80.4 mmol) to yield the *title compound* **3.41** as a yellow powder (4.96 g, 86%), m.p. 162-163°C; Found: MH⁺ 360.0315. C₁₁H₁₄IN₅O requires MH 360.0321; ν_{\max} (KBr/cm⁻¹) 3339, 3064, 3040, 2971, 2928, 2871, 1794, 1611, 1527, 1471, 1348, 1322, 1237, 1191, 1152 and 1111; δ_{H} 1.33 (6H, d, *J* 6.9, CHMe₂), 3.24 (1H, septet, *J* 6.9, CHMe₂), 3.63 and 4.64 (each 2H, t, *J* 6.5, CH₂CH₂), 8.14 and 8.71 (each 1H, s, 2-CH and 8-CH) and 8.93 (1H, s, NHCO); δ_{C} 19.5 (CH₃), 20.05 (CH₂I), 36.0 (CHMe₂), 45.8 (NCH₂), 122.5 and 143.1 (ArC), 149.6 and 151.3 (C-2 and C-8), 152.7 (ArC) and 176.4 (CO); *m/z* 359 (M⁺, 20%), 289 (20), 205 (20), 135 (100) and 108 (15).

*N*9-(3-Bromopropyl)-*N*6-(2-methylpropanoyl)adenine, 3.42



Prepared following method A, using *N*6-(2-methylpropanoyl)adenine **2.91** (4.5 g, 22.0 mmol), triphenylphosphine (6.91 g, 26.3 mmol), 3-bromo-1-propanol (2.39 cm³, 3.66 g, 26.3 mmol), dioxane (170 cm³) and DIAD (5.19 cm³, 5.33 g, 26.3 mmol). Purification by column chromatography (hexane:ethyl acetate 4:1 v/v) gave the *title compound* **3.42** as a white solid (5.42 g, 76%), m.p. 110-111°C (from toluene). Found: MH⁺ (ES⁺) 326.0621. C₁₂H₁₆BrN₅O requires: MH 326.0616; ν_{\max} (KBr/cm⁻¹) 3283, 3137, 3068, 3047, 2970, 2930, 1689, 1663, 1485, 1406, 1350, 1234 and 1227; δ_{H} 1.31 (6H, d, *J* 6.5, CHMe₂), 2.49 (1H, septet, *J* 6.5, CHMe₂), 3.30 (2H, apparent quintet, *J* 6.8, CH₂CH₂CH₂), 3.37 (2H, t, *J* 6.2, CH₂Br), 4.49 (2H, t, *J* 6.6, NCH₂), 8.14 and 8.73 (each 1H, s, 2-CH and 8-CH) and 8.85 (1H, s, NHCO); δ_{C} 19.25 (CH₃), 29.5 and 31.7 (CH₂), 36.0 (CHMe₂), 42.3 (CH₂), 122.4 (ArC), 143.1 (CH), 149.5 and 151.7 (ArC), 152.5 (CH) and 176.6 (CO); *m/z* 325 (M⁺, 20%), 257 (20), 205 (20), 176 (40), 149 (100) and 71 (38).

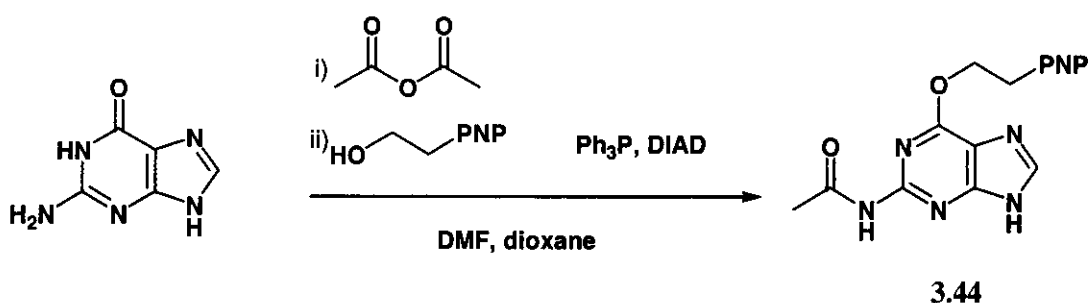
*N*9-(3-Iodopropyl)-*N*6-(2-methylpropanoyl)adenine, 3.43



Prepared following method B, using *N*9-(3-bromopropyl)-*N*6-(2-methylpropanoyl)adenine **3.42** (5.3 g, 16.3 mmol) and sodium iodide (12.2 g, 81.5 mmol) to yield the *title compound* **3.43** as a yellow gum (4.93 g, 81%). Found: MH⁺ (ES⁺) 374.0473. C₁₂H₁₆IN₅O requires:

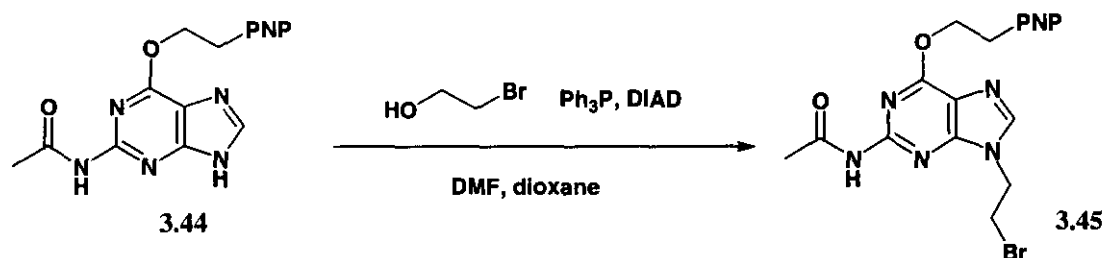
MH 374.0478; ν_{\max} (film/ cm^{-1}) 3413, 2981, 1610, 1588, 1459 and 908; δ_{H} 1.31 (6H, d, J 6.7, CHMe_2), 2.43 (1H, septet, J 6.7, CHMe_2), 3.12 (2H, t, J 6.6, CH_2I), 3.24 (2H, apparent quintet, J 6.6, $\text{CH}_2\text{CH}_2\text{CH}_2$), 4.42 (2H, t, J 5.6, NCH_2), 8.09 and 8.73 (each 1H, s, 2-CH and 8-CH), 8.75 (1H, s, NHCO); δ_{C} 1.65 (CH_2), 19.2 (CH_3), 32.3 (CH_2), 36.1 (CHMe_2), 44.5 (CH_2), 122.3 (ArC), 142.9 (CH), 149.4 and 151.6 (ArC), 152.57 (CH) and 176.9 (CO); m/z 373 (M^+ , 10%), 277 (80), 199 (28), 149 (54) and 77 (100).

***N*2-Acetyl-*O*6-[2-(4-nitrophenyl)ethyl]guanine **3.44**¹⁰⁰**



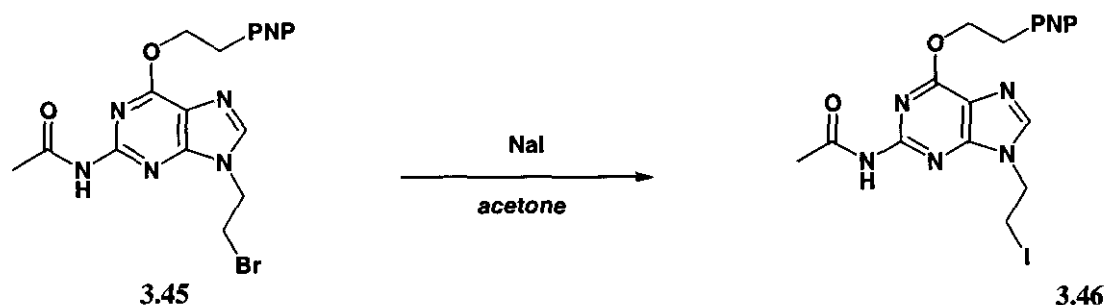
To a suspension of guanine (10 g, 66.2 mmol) in DMF (150 cm^3) acetic anhydride (18.7 cm^3 , 20.27 g, 198.5 mmol) was added dropwise at room temperature. The mixture was then heated at reflux for 4 h to yield a clear solution. After evaporation of the solvents under reduced pressure, the residue was washed with saturated aqueous sodium hydrogen carbonate (100 cm^3) and cold ethanol (25 cm^3), and dried with P_2O_5 under vacuum overnight. The solid was suspended with 2-(4-nitrophenyl)ethanol (16.6 g, 99.3 mmol) and triphenylphosphine (26.0 g, 99.3 mmol) in dioxane (200 cm^3) and DIAD (20.1 g, 19.6 cm^3 , 99.3 mmol) was added dropwise at 0°C under argon over 3 h. The mixture was stirred at room temperature overnight to yield a pale yellow solution to which water (100 cm^3) was added and the mixture heated at reflux for 2 h. After cooling, solvents were evaporated under reduced pressure and the residue purified by column chromatography (DCM:MeOH, 90:10 v/v) to afford the title compound **3.44** (12.0 g, 53%), m.p. $>250^\circ\text{C}$; δ_{H} (300 MHz; $\text{DMSO}-d_6$) 2.17 (3 H, s, CH_3), 3.32 and 4.77 (each 2H, t, J 6.8 Hz, CH_2CH_2), 7.66 (2H, d, J 8.3 Hz, ArH), 8.04 (1H, s, 9-NH), 8.17 (3H, m, 8-CH and ArH), 10.31 (1H, s, CONH).

***N*9-(2-Bromoethyl)-*N*2-acetyl-*O*6-[2-(4-nitrophenyl)ethyl]guanine, 3.45**



Prepared following method A, using *N*2-acetyl-*O*6-[2-(4-nitrophenyl)ethyl]guanine **3.44** (5.0 g, 14.6 mmol), 2-bromoethanol (1.24 cm³, 2.19 g, 17.5 mmol), triphenylphosphine (4.6 g, 17.5 mmol), dioxane (100 cm³) and DIAD (3.54 g, 3.45 cm³, 17.5 mmol). Purification by flash chromatography (EtOAc:hexane, 4:1 v/v) gave the *title compound* **3.45** as a white solid (4.39 g, 67%), m.p. 181-182°C. Found: MH⁺ (FAB) 449.0573. C₁₇H₁₇⁷⁹BrN₆O₄ requires: MH 449.0579; ν_{\max} (KBr/cm⁻¹) 3206, 3133, 1665, 1610, 1589, 1510, 1460, 1415, 1383, 1352, 1327, 1309, 1226 and 1025; δ_{H} (DMSO-*d*₆) 1.97 (3H, s, CH₃), 3.28 (2H, t, *J* 6.8, ArCH₂), 3.95 and 4.55 (each 2H, t, *J* 6.0, NCH₂CH₂Br), 4.77 (2H, t, *J* 6.8, OCH₂), 7.60 and 8.20 (each 2H, d, *J* 8.2, ArH), 8.29 (1H, s, 8-CH), 10.42 (1H, s, NHCO); δ_{C} (DMSO-*d*₆) 24.7 (CH₃), 31.0, 34.2, 44.85 and 66.4 (CH₂), 116.65 (ArC), 123.4, 130.3 and 142.8 (ArCH), 146.21, 146.4, 152.0, 152.9 and 159.6 (ArC) and 169.10 (CO); *m/z* 449 (MH⁺, 65%), 343 (20), 300 (75), 258 (35), 178 (50), 151 (100) and 133 (52).

***N*2-acetyl-*N*9-(2-Iodoethyl)-*O*6-[2-(4-nitrophenyl)ethyl]guanine, 3.46**



Prepared using a modification of method B. *N*2-Acetyl-*N*9-(2-bromoethyl)-*O*6-[2-(4-nitrophenyl)ethyl]guanine **3.45** (0.77 g, 1.72 mmol) and dry sodium iodide (1.29 g, 8.58 mmol) in dry acetone (50 cm³) was heated at reflux in the dark (aluminium foil) under argon overnight. After cooling, the acetone was removed under reduced pressure and the

residue taken up in dichloromethane (50 cm³) and water (50 cm³). The organic layer was separated and washed with aqueous sodium thiosulfate solution (2% w/v, 2 x 25 cm³), dried (MgSO₄) and the solvents were removed under reduced pressure to yield the *title compound* **3.46** as a yellow gum (0.72 g, 85%). Found: MH⁺ (FAB) 497.0412. C₁₇H₁₇IN₆O₄ requires: MH 497.0408; ν_{\max} (KBr/cm⁻¹) 3387, 3093, 1685, 1677, 1656, 1605, 1515, 1493, 1381, 1344, 1327, 1213, 1048 and 1023; δ_{H} (DMSO-*d*₆) 2.25 (3H, s, CH₃), 3.32 (2H, t, *J* 6.8, ArCH₂), 3.70 and 4.51 (each 2H, t, *J* 6.6, NCH₂CH₂I), 4.79 (2H, t, *J* 6.8, OCH₂), 7.56 and 8.18 (each 2H, d, *J* 8.3, ArH), 8.26 (1 H, s, 8-CH), 10.42 (1H, s, NHCO); δ_{C} (DMSO-*d*₆) 3.65 (CH₂), 24.7 (CH₃), 34.2, 45.3 and 66.35 (CH₂), 116.8 (ArC), 123.3, 130.3 and 142.6 (ArCH), 146.2, 146.4, 152.9, 152.8 and 159.6 (ArC) and 169.0 (CO); *m/z* 497 (MH⁺, 75%), 348 (55), 279 (26), 193 (65), 151 (100) and 107 (73).

General procedure for conjugate radical addition to oxazolidinone **3.23** (method C)

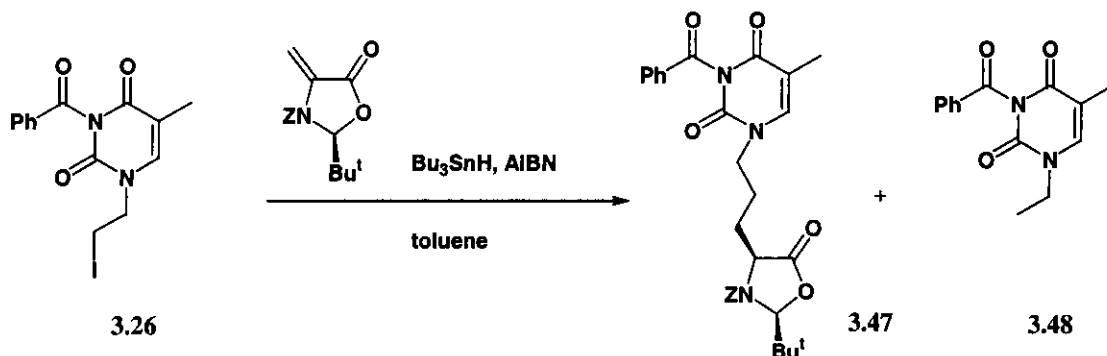
Tributyltin hydride (1.2 mol equiv.) was added dropwise *via* syringe pump over 2 h to the appropriate iodoalkyl derivative (1.0 mol equiv.), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (1.2 mol equiv.) and AIBN (0.1 mol equiv.) in degassed toluene (200 cm³), at 80°C and under a positive atmosphere of argon. Heating and stirring were continued until reflux and for a further 12 h. After cooling, the toluene was removed under reduced pressure and the residue purified by flash column chromatography (EtOAc:hexane, 1:4 to 4:1 v/v) to give the conjugate adduct.

General procedure for conjugate radical addition to oxazolidinone **3.23** (method D)

The appropriate iodoalkyl derivative (1.0 mol equiv.), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (2 mol equiv.), tributyltin chloride (0.3 mol equiv.), sodium cyanoborohydride (2 mol equiv.) and AIBN (0.1 mol equiv) in *tert*-butanol (40 cm³/g of **3.23**) were heated at reflux under a positive atmosphere of argon for 40 h. After cooling, the solvent was removed under reduced pressure and the residue purified by

flash column chromatography (EtOAc:hexane, 1:4 to 4:1 v/v) to yield the conjugate adduct.

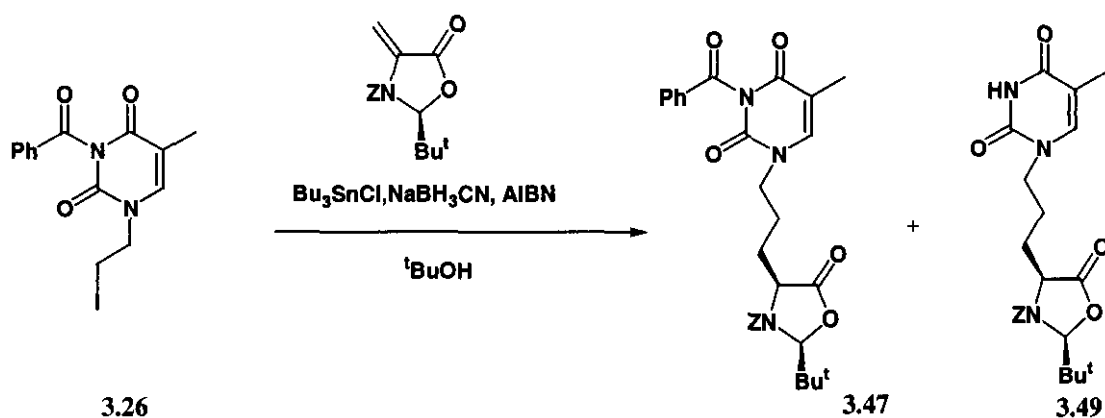
(2*S*,4*S*)-4-[3-(3-Benzoyl-1-thiminyl)propyl]-3-benzyloxycarbonyl-2-*tert*-butyl oxazolidin-5-one, 3.47



Performed following method C, using *N*3-benzoyl-*N*1-(2-iodoethyl)thymine **3.26** (0.66 g, 17.2 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (497 mg, 17.2 mmol), AIBN (*ca.* 10 mg) and tributyltin hydride (0.555 cm^3 , 0.60 g, 20.6 mmol) to give the *conjugate adduct* **3.47** as a colourless oil (244 mg, 26%) and 3-benzoyl-1-ethylthymine **3.48** as a white solid (106 mg, 24%), m.p. 169-171°C. (2*S*,4*S*)-4-[3-(3-Benzoyl-1-thiminyl)propyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one, **3.47**: Found: MH^+ (CI) 548.2387. $\text{C}_{30}\text{H}_{33}\text{N}_3\text{O}_7$ requires: MH 548.2397; ν_{max} (film/ cm^{-1}) 3431, 2361, 2342, 1790, 1749, 1701, 1657, 1440 and 1266; δ_{H} 0.94 (9H, s, CMe_3), 1.74-2.04 (7H, m, 2 x $\text{NCH}_2\text{CH}_2\text{CH}_2$ and $\text{CH}=\text{CCH}_3$), 3.69 and 3.81 (each 1H, m, NCH_2), 4.31 (1H, t, J 6.8, CHCH_2), 5.17 (2H, s, CH_2Ph), 5.56 (1H, s, CHBu^t), 7.11 (1H, s, $\text{CH}=\text{CCH}_3$), 7.34-7.38 (5H, m, ArH), 7.49 (2H, m, ArH), 7.64 (1H, m, ArH) and 7.91 (2H, m, ArH); δ_{C} 12.4 ($\text{CH}=\text{CCH}_3$), 24.9 (CMe_3), 25.8 ($\text{NCH}_2\text{CH}_2\text{CH}_2$), 29.9 (CHCH_2), 36.9 (CMe_3), 47.7 (NCH_2), 56.6 (CHCH_2), 68.7 (CH_2Ph), 96.5 (CHBu^t), 110.9 ($\text{CH}=\text{CCH}_3$), 128.6, 128.8, 128.8, 129.1, 130.4 and 131.7 (ArCH), 134.95 and 135.0 (ArC), 139.9 ($\text{CH}=\text{CCH}_3$), 149.8, 156.1, 163.1, 169.0 and 172.3 (CO); m/z (EI) 547 (M^+ , 100%), 490 (50), 442 (30), 393 (60), 315 (70) and 286 (45). *N*3-Benzoyl-*N*1-ethylthymine **3.48**: Found: (MH^+) (CI) 259.1083. $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_3$ requires: MH 259.1082; ν_{max} (KBr/ cm^{-1}) 3192, 3080, 3069, 2984, 2960, 2744, 2620, 2464, 2095, 1986, 1693, 1644, 1366, 1346, 1266, 1248 and 1193; δ_{H} 1.30 (3H, t, J 7.2, CH_2CH_3), 1.95 (3H, s, $\text{CH}=\text{CCH}_3$), 3.77 (2H, q, J 7.2, CH_2CH_3), 7.12

(1H, s, CH=CCH₃), 7.49 (2H, m, ArH), 7.64 (1H, m, ArH) and 7.91 (2H, m, ArH); *m/z* 258 (M⁺, 15%), 230 (100) and 188 (40).

(2*S*,4*S*)-4-[3-(3-Benzoyl-1-thyminy)propyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one, 3.47 and **(2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[3-(1-thyminy)propyl]oxazolidin-5-one, 3.49**

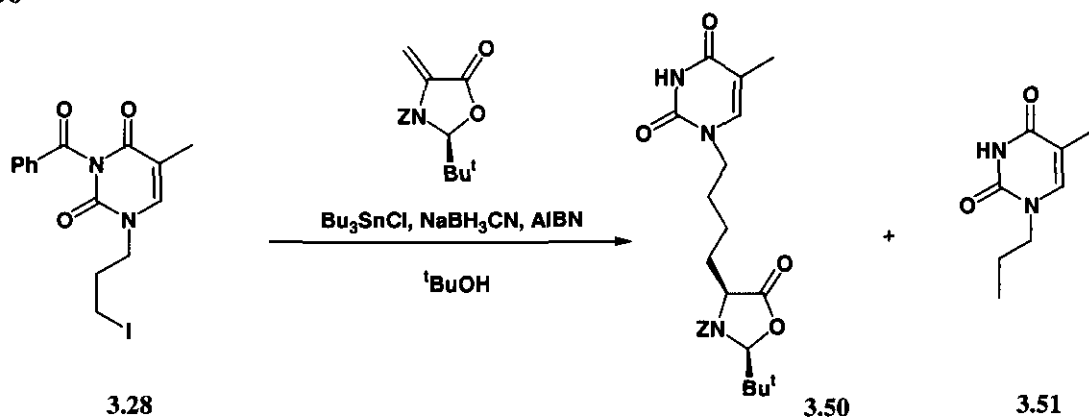


Performed following method D, using *N*3-benzoyl-*N*1-(2-iodoethyl)thymine **3.26** (1.13 g, 2.94 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (1.70 g, 5.89 mmol), tributyltin chloride (0.239 cm³, 0.287 g, 0.882 mmol), sodium cyanoborohydride (0.370 g, 5.89 mmol) and AIBN (0.29 mmol), but heating at reflux for 16 h to yield the *conjugate adduct* **3.47** as a colourless oil (1.29 g, 24%) identical with the sample prepared by method C, and the *debenzoylated conjugate adduct* **3.49** as a white solid (0.391 g, 30%), m.p. (decomp.) 78-80°C. No reduced products were isolated. (2*S*,4*S*)-3-Benzoyloxycarbonyl-2-*tert*-butyl-4-[3-(1-thyminy)propyl]oxazolidin-5-one, **3.49**: Found: MH⁺ (CI) 444.2132. C₂₃H₂₉N₃O₆ requires: MH 444.2134; ν_{max} (KBr/cm⁻¹) 3204, 3037, 2964, 1792, 1708, 1680, 1467, 1397, 1363, 1348, 1229, 1198 and 1125; δ_{H} 0.95 (9H, s, CMe₃), 1.85-1.99 (7H, m, CH₂CH₂ and CH=CCH₃), 3.68 and 3.76 (each 1H, m, NCH₂), 4.32 (1H, t, *J* 6.8 Hz, CHCH₂), 5.17 and 5.18 (2H, 2 × d, *J* 11.9, CH₂Ph), 5.56 (1H, s, CHBu^t), 7.00 (1H, s, CH=CCH₃), 7.34-7.38 (5H, m, ArH) and 9.57 (1H, s, NH); δ_{C} 12.3 (CH=CCH₃), 24.9 (CMe₃), 25.8 (NCH₂CH₂CH₂), 29.8 (CHCH₂), 36.9 (CMe₃), 47.4 (NCH₂), 56.7 (CHCH₂), 68.6 (PhCH₂), 96.5 (CHBu^t), 110.8 (CH=CCH₃), 128.6, 128.7 and 128.8 (ArH), 135.0 (ArC), 140.2 (CH=CCH₃), 172.3, 171.2, 164.5 and 156.1 (CO); *m/z*

(EI) 443 (M^+ , 60%), 386 (70), 308 (75), 286 (100), 264 (35), 250 (35), 208 (80) and 194 (48).

When the reaction time was extended to 40 h, using *N*3-benzoyl-*N*1-(2-iodoethyl)thymine **3.26** (6.84 g, 17.8 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one (10.3 g, 35.6 mmol), tributyltin chloride (1.45 cm³, 1.74 g, 5.34 mmol), sodium cyanoborohydride (2.24 g, 35.6 mmol) and AIBN (1.78 mmol), purification by column chromatography gave only the adduct **3.49** as a white solid (3.68 g, 47%), data as above. Reduced products were not isolated.

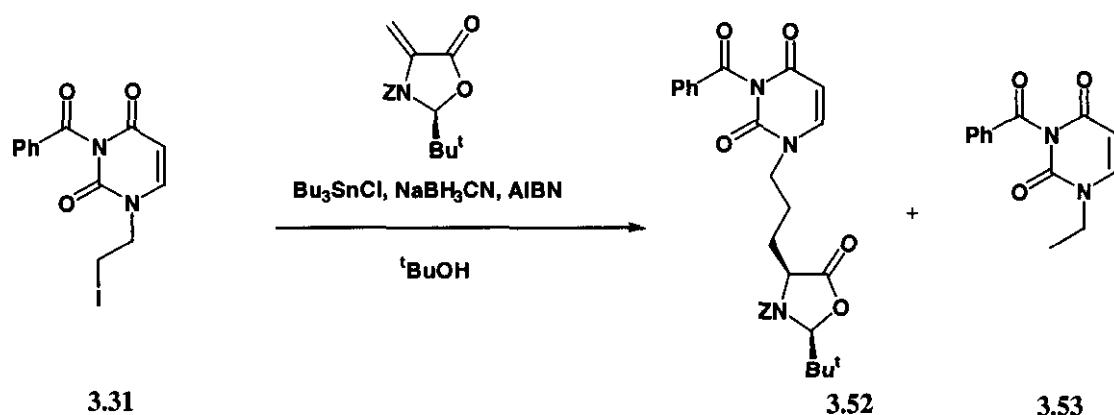
(2*S*,4*S*)-3-Benzyloxycarbonyl-4-[4-(1-thiminyl)butyl]-2-*tert*-butyloxazolidin-5-one, **3.50**



Prepared following method D, using *N*3-benzoyl-*N*1-(3-iodopropyl)thymine **3.28** (3.12 g, 7.84 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (4.53 g, 15.7 mmol), tributyltin chloride (0.638 cm³, 0.765 g, 2.35 mmol), sodium cyanoborohydride (0.98 g, 15.7 mmol) and AIBN (0.78 mmol) to yield the *debenzoylated conjugate adduct* **3.50** as a thick oil (900 mg, 25%) and *N*1-propylthymine¹⁰⁸ **3.51** as a white solid (276 mg, 21%), m.p. 134-135°C. (2*S*,4*S*)-3-Benzyloxycarbonyl-4-[4-(1-thiminyl)butyl]-2-*tert*-butyloxazolidin-5-one **3.50**: Found: MH^+ 458.2287. C₂₄H₃₁N₃O₆ requires: MH 458.2291; ν_{\max} (film/cm⁻¹) 3489, 3201, 3068, 2964, 1789, 1710, 1690, 1480, 1398, 1348, 1289, 1269, 1225, 1125, 1043 and 1013; δ_H 0.95 (9H, s, CMe₃), 1.56-2.05 (9H, m, CH(CH₂)₃CH₂N and CH=CCH₃), 3.49-3.69 (2H, m, NCH₂), 4.23-4.28 (1H, t, *J* 6.8, CHCH₂), 5.17 (2H, s, CH₂Ph), 5.55 (1H, s, CHBu^{*t*}), 6.89 (1H, s, CH=CCH₃), 7.32-7.44 (5H, m, ArH) and 9.08 (1H, s, NH); δ_C 12.3 (CH=CCH₃), 23.2 (CH₂), 24.9 (CMe₃), 28.4 and 32.6 (CH₂), 37.0 (CMe₃), 48.2 (NCH₂), 56.8 (CHCH₂), 68.5 (CH₂Ph), 96.4 (CHBu^{*t*}),

110.7 (CCH₃), 128.5, 128.55 and 128.7 (ArCH), 135.2 (ArC), 140.4 (CH=CCH₃), 150.8, 156.0, 164.3 and 172.6 (CO); *m/z* 457 (EI) (*M*⁺, 10%), 400 (20), 300 (30), 91 (25), 84 (100) and 47 (20). *N*1-Propylthymine **3.51**¹⁰⁸: Found: *MH*⁺ 169.0980. C₈H₁₂N₂O₂ requires: *MH* 169.0977; *v*_{max}(KBr/cm⁻¹) 3163, 3099, 3027, 2970, 1704, 1649 and 1245; *δ*_H 0.94 (3H, t, *J* 7.5, CH₂CH₃), 1.71 (2H, apparent sextet, *J* 7.3, NCH₂CH₂CH₃), 1.93 (3H, s, CH=CCH₃), 2.91 (2H, t, *J* 6.3, NCH₂CH₂), 6.99 (1H, s, CH=CCH₃) and 9.37 (1H, s, NH); *δ*_C 10.9 (CH₂CH₃), 12.3 (CH=CCH₃), 22.35 (CH₂CH₃), 50.05 (NCH₂), 110.5 (CH=CCH₃), 140.5 (CH=CCH₃), 151.1 and 164.4 (CO); *m/z* (EI) 168 (*M*⁺, 90%), 126 (90), 96 (100), 55 (37) and 41 (40).

(2*S*,4*S*)-4-[3-(3-Benzoyl-1-uracilyl)propyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one, **3.52**

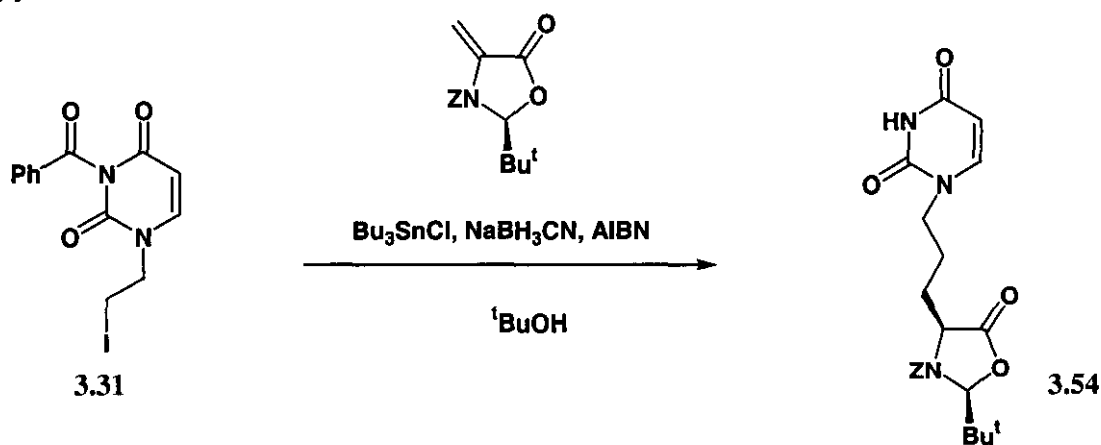


Prepared following method D, using *N*3-benzoyl-*N*1-(2-iodoethyl)uracil **3.31** (0.76 g, 2.05 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (1.19 g, 4.11 mmol), tributyltin chloride (0.167 cm³, 0.201 g, 0.616 mmol), sodium cyanoborohydride (0.258 g, 4.11 mmol) and AIBN (0.205 mmol), but heating at reflux for 7 h to yield the *conjugate adduct* **3.52** as a colourless oil (510 mg, 47%) and *N*3-benzoyl-*N*1-ethyluracil **3.53** as a white amorphous gum (230 mg, 46%) that was incompletely characterized. No debenzoylated products were observed in the mixture. (2*S*,4*S*)-4-[3-(3-Benzoyl-1-uracilyl)propyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one **3.52**: Found: *MH*⁺ (CI) 534.2237. C₂₉H₃₁N₃O₇ requires: *MH* 534.2240; *v*_{max}(film/cm⁻¹) 3404, 3369, 1790, 1749, 1704, 1665, 1497, 1439, 1392, 1347, 1255, 1235 and 1041; *δ*_H 0.94 (9H, s, Bu^t), 1.82-2.01 (4H, m, CHCH₂CH₂), 3.69-3.85 (2H, m, NCH₂), 4.30 (1H, t, *J*

6.8, CHCH₂), 5.16 (2H, s, CH₂Ph), 5.56 (1H, s, CHBu^t), 5.75 (1H, d, *J* 7.9, CH=CHCO), 7.24-7.40 (6H, m, ArH and CH=CHCO), 7.46-7.52 (2H, m, ArH), 7.61-7.67 (1H, m, ArH) and 7.90 (2H, m, ArH); δ_C 24.9 (CMe₃), 25.7 (CH₂CH₂CH₂), 29.8 (CHCH₂), 36.9 (CMe₃), 48.0 (NCH₂), 56.6 (CHCH₂), 68.7 (CH₂Ph), 96.5 (CHBu^t), 102.15 (CHCO), 128.4, 128.6, 128.8, 128.8, 129.2 and 130.4 (ArCH), 131.5 and 135.1 (ArC), 144.1 (CH=CHCO), 149.8, 156.1, 162.4, 168.8 and 172.3 (CO); *m/z* 533 (MH⁺, 20%), 476 (30), 404 (25), 376 (50), 301 (40) and 198 (50). *N*3-Benzoyl-*N*1-ethyluracil **3.53**: ν_{max}(film/cm⁻¹) 3413, 3058, 2984, 2328, 2178, 1788, 1749, 1665, 1601, 1485, 1439, 1391, 1346, 1266, 1178 and 1122; δ_H 1.29 (3H, t, *J* 7.2, NCH₂CH₃), 3.79 (2H, q, *J* 7.2, NCH₂CH₃), 5.81 (1H, d, *J* 7.9, 5-CH), 7.20-7.52 (4H, m, ArH and 6-CH), 7.89 (2H, m, ArH); *m/z* 244 (M⁺, 5%), 216 (30), 199 (20), 183 (15), 105 (100) and 77 (88).

(2*S*,4*S*)-3-Benzoyloxycarbonyl-4-[3(1-uracilyl)propyl]-2-*tert*-butyloxazolidin-5-one,

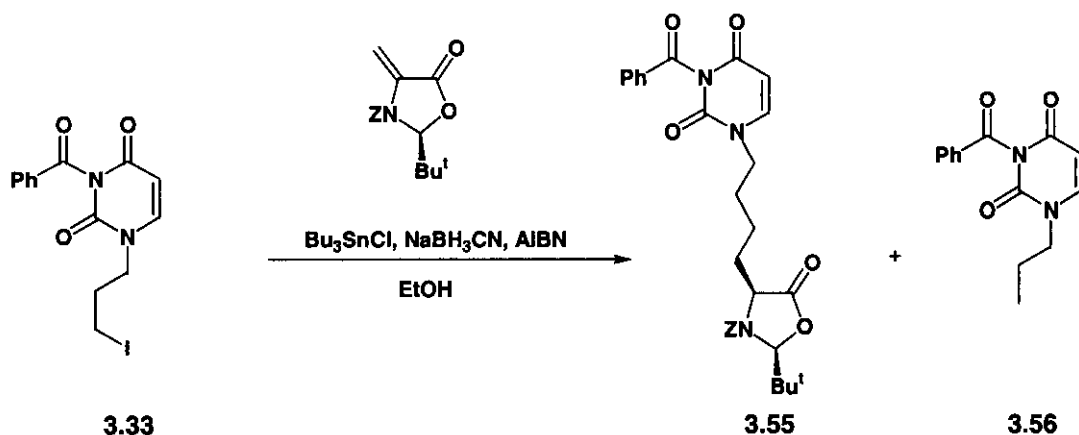
3.54



Prepared following method D, using *N*3-benzoyl-*N*1-(2-iodoethyl)uracil **3.31** (5.45 g, 14.7 mmol), (2*S*)-3-benzoyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (8.51 g, 29.5 mmol), tributyltin chloride (1.20 cm³, 1.44 g, 4.42 mmol), sodium cyanoborohydride (1.85 g, 29.5 mmol) and AIBN (1.47 mmol) to yield the *debenzoylated conjugate adduct* **3.54** as a colourless oil (3.24 g, 51%). No benzoylated product was isolated; reduction product was present but not purified from this experiment. (2*S*,4*S*)-3-Benzoyloxycarbonyl-4-[3-(1-uracilyl)propyl]-2-*tert*-butyloxazolidin-5-one **3.54**: Found: MNH₄⁺ (ES⁺) 447.2255. C₂₂H₂₇N₃O₆ requires: MNH₄ 447.2244; ν_{max}(film/cm⁻¹) 3691, 3055, 2360, 2342, 1791, 1713, 1689 and 1266; δ_H 0.92 (9H, s, Bu^t), 1.83-2.10 (4H, m, CHCH₂CH₂), 3.26-3.82 (2H, m, NCH₂), 4.43 (1H, t, *J* 6.8, CHCH₂), 5.16 (2H, s, CH₂Ph), 5.54 (1H, s,

CHBu^t), 5.82 (1H, d, J 7.5, $\text{CH}=\text{CHCO}$), 7.32-7.34 (6H, m, ArH and $\text{CH}=\text{CHCO}$) and 9.92 (1H, s, NH); δ_{C} 24.9 (CMe_3), 26.7 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 28.9 (CHCH_2), 36.8 (CMe_3), 47.6 (NCH_2), 56.7 (CHCH_2), 68.9 (CH_2Ph), 96.8 (CHBu^t), 102.5 (CHCO), 128.7, 135.0 (ArCH), 146.15 and 147.1 (ArC), 151.4 ($\text{CH}=\text{CHCO}$), 156.4, 165.5, 171.0 and 173.3 (CO); m/z 430 (MH^+ , 30%), 279 (20), 254 (100), 238 (30) and 220 (90).

(2*S*,4*S*)-4-[4-(3-Benzoyl-1-uracilyl)butyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one, 3.55

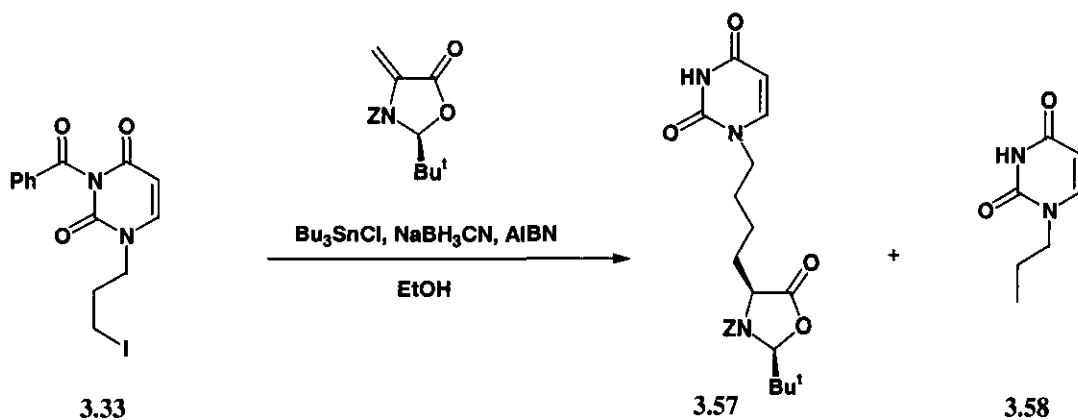


Prepared following a modified method D, using *N*3-benzoyl-*N*1-(3-iodopropyl)uracil 3.33 (2.40 g, 6.25 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one 3.23 (1.51 g, 5.21 mmol), tributyltin chloride (0.424 cm³, 0.509 g, 1.56 mmol), sodium cyanoborohydride (0.427 g, 6.79 mmol) and AIBN (0.52 mmol) but heated at reflux in degassed ethanol (50 cm³) for 8 h to yield the *conjugate adduct* as a colourless oil (598 mg, 21%) and 3-benzoyl-1-propyluracil as a white gum (362 mg, 27%) that was incompletely characterized.

(2*S*,4*S*)-4-[4-(3-Benzoyl-1-uracilyl)butyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one 3.55: Found: MH^+ (CI) 548.2390. $\text{C}_{30}\text{H}_{33}\text{N}_3\text{O}_7$ requires: MH 548.2397; $\nu_{\text{max}}(\text{KBr}/\text{cm}^{-1})$ 2962, 2362, 1791, 1749, 1703, 1664, 1438, 1371, 1348, 1256 and 1235; δ_{H} 1.00 (9H, s, CMe_3), 1.64-2.02 (6H, m, $\text{CH}(\text{CH}_2)_3\text{CH}_2$), 3.74 (2H, m, NCH_2), 4.31 (1H, t, J 7.0, CHCH_2), 5.21 (2H, s, CH_2Ph), 5.60 (1H, s, CHBu^t), 5.81 and 7.25 (each 1H, d, J 7.4, $\text{CH}=\text{CHCO}$), 7.42-7.44 (5H, m, ArH), 7.55 (2H, m, ArH) 7.70 (1H, m, ArH) and 7.97 (2H, m, ArH); δ_{C} 22.0 (CH_2), 24.8 (CMe_3), 28.1 and 32.4 (CH_2), 36.81 (CMe_3), 48.7 (NCH_2), 53.4 (CHCH_2), 68.3 (CH_2Ph), 96.3 (CHBu^t), 101.9 (CHCO), 128.4, 128.6, 128.7, 129.1 and 130.3 (ArCH), 131.4 (ArC), 135.0 (ArCH), 135.1 (ArC), 144.2

(CH=CHCO), 149.6, 155.8, 162.35, 168.8 and 172.4 (CO); m/z 547 (M^+ , 20%), 490 (50), 446 (30), 418 (50), 390 (60), 286 (40) and 198 (100). *N*3-Benzoyl-*N*1-propyluracil **3.56**: δ_H 0.96 (3H, t, J 7.5, CH_2CH_3), 1.72 (2H, apparent sextet, J 7.3, $NCH_2CH_2CH_3$), 3.68 (2H, t, J 7.3, NCH_2), 5.80 and 7.20 (each 1H, d, J 7.1, $CH=CHCO$) and 7.47-7.68 (5H, m, ArH).

(2*S*,4*S*)-3-Benzoyloxycarbonyl-4-[4-(1-uracilyl)butyl]-2-*tert*-butyloxazolidin-5-one, 3.57



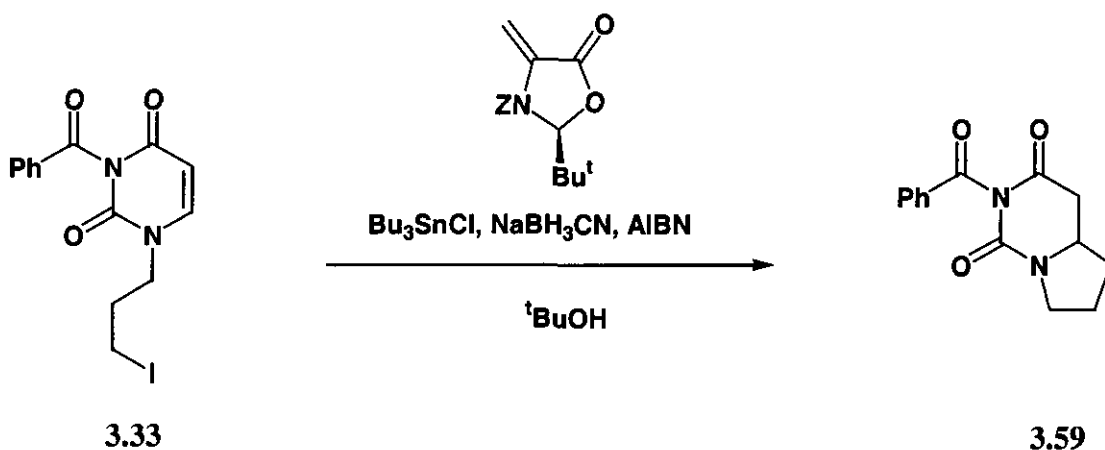
Prepared following method D, using *N*3-benzoyl-*N*1-(3-iodopropyl)uracil **3.33** (1.98 g, 5.16 mmol), (2*S*)-3-benzoyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (2.98 g, 10.3 mmol), tributyltin chloride (0.420 cm³, 503 mg, 1.55 mmol), sodium cyanoborohydride (648 mg, 10.3 mmol) and AIBN (0.516 mmol) to yield the *debenzoylated conjugate adduct* **3.57** as an amorphous solid (1.00 g, 44%), m.p. (decomp.) 151-153°C, and *N*1-propyluracil¹⁰⁹ **3.58** as a white gum (0.405 g, 51%). (2*S*,4*S*)-3-Benzoyloxycarbonyl-4-[4-(1-uracilyl)butyl]-2-*tert*-butyloxazolidin-5-one **3.57**:

Found: MH^+ 444.2125. $C_{23}H_{29}N_3O_6$ requires: MH 444.2134; δ_H (CD_3OD) 0.93 (9H, s, CMe_3), 1.52-2.01 (6H, m, $CH(CH_2)_3CH_2N$), 3.58-3.73 (2H, m, NCH_2), 4.35 (1H, t, J 7.5, $CHCH_2$), 5.16 (2H, s, CH_2Ph), 5.56 (1H, s, $CHBu^t$), 5.62 (1H, d, J 7.7, $CH=CHCO$) and 7.30-7.50 (6H, m, ArH and $CH=CHCO$); δ_C (CD_3OD) 24.2 (CH_2), 25.4 (CMe_3), 29.2 and 33.8 (CH_2), 37.8 (CMe_3), 48.5 (NCH_2), 58.2 ($CHCH_2$), 69.4 (CH_2Ph), 97.8 ($CHBu^t$), 102.2 ($CH=CHCO$), 128.75, 129.5 and 129.6 (ArCH), 137.1 (ArC), 147.3 ($CH=CHCO$), 152.8, 157.9, 166.8 and 174.6 (CO); m/z 444 (MH^+ , 80%) and 430 (20). *N*1-Propyluracil **3.58**¹⁰⁹: Found: M^+ (EI) 154.0734. $C_7H_{10}N_2O_2$ requires: M 154.0742; δ_H 0.91 (3H, t, J 7.3, CH_2CH_3), 1.72 (2H, sextet, J 7.3, $CH_2CH_2CH_3$), 3.70 (2H, t, J 7.3 Hz, NCH_2), 5.72 (1H,

d, J 7.9, CH=CHCO), 7.16 (1H, d, J 7.9, CH=CHCO) and 9.20 (1H, s, NH); δ_{C} 10.9 (CH₂CH₃), 22.3 (CH₂CH₃), 50.45 (NCH₂), 102.0 (C-5), 144.7 (C-6), 164.0 and 171.2 (CO); m/z 154 (M⁺, 50%), 126 (15), 112 (60), 82 (100), 69 (50) and 55 (40).

This experiment was repeated using *N*3-benzoyl-*N*1-(3-iodopropyl)uracil **3.33** (1.98 g, 5.16 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (7.45 g, 25.8 mmol, 5 mol equiv.), tributyltin chloride (0.420 cm³, 503 mg, 1.55 mmol), sodium cyanoborohydride (648 mg, 10.3 mmol) and AIBN (0.516 mmol) to yield the *debenzoylated conjugate adduct* **3.57** as an amorphous solid (1.42 g, 62%), identical to the above sample.

3-Benzoyloctahydropyrrolo[1,2-*c*]pyrimidine-2,4-dione, **3.59**

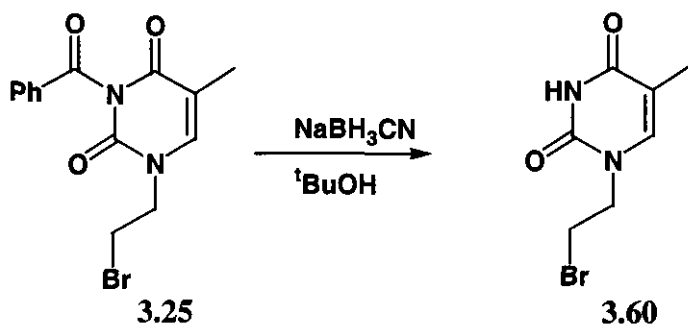


Prepared following method D, using *N*3-benzoyl-*N*1-(3-iodopropyl)uracil **3.33** (0.86 g, 2.24 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (777 mg, 2.69 mmol), tributyltin chloride (0.182 cm³, 219 mg, 0.67 mmol), sodium cyanoborohydride (42 mg, 0.67 mmol) and AIBN (0.2 mmol) but heated at reflux for 30 min. to yield recovered oxazolidinone **3.23** (640 mg, 82%) and uracil **3.33** (690 mg, 80%), and the *title compound* **3.59** (99 mg, 17%; 87% based on recovered uracil **3.33**) as a white amorphous solid, m.p. 157-158°C; Found: MH⁺ (CI) 259.1084. C₁₄H₁₄N₂O₃ requires: MH 259.1083; ν_{max} (KBr/cm⁻¹) 2963, 2926, 1743, 1704, 1681, 1438, 1370, 1349, 1278, 1258, 1240 and 980; δ_{H} 1.64-1.76 (1H, m, COCH₂CHCHH), 1.94-2.00 and 2.09-2.15 (each 1H, dddd, J 2.4, 4.8, 7.0, 9.7 and 11.9, NCH₂CH₂), 2.32-2.38 (1H, m, COCH₂CHCHH), 2.57 (1H, dd, J 13.2 and 15.9 Hz, COCHH), 2.95 (1H, dd, J 3.9 and 16.0, COCHH), 3.50-3.71 (2H, m, NCH₂), 3.91-3.95 (1H, m, NCH), 7.49 (2H, m, ArH), 7.62 (1H, m, ArH)

and 7.89-7.92 (2H, m, ArH); δ_{C} 23.2 (NCH₂CH₂CH₂), 33.2 (CHCH₂), 38.3 (COCH₂), 45.3 (NCH₂), 52.9 (CH), 129.2 and 130.5 (ArCH), 132.7 (ArC), 134.5 (ArCH), 149.9, 168.9 and 170.0 (CO).

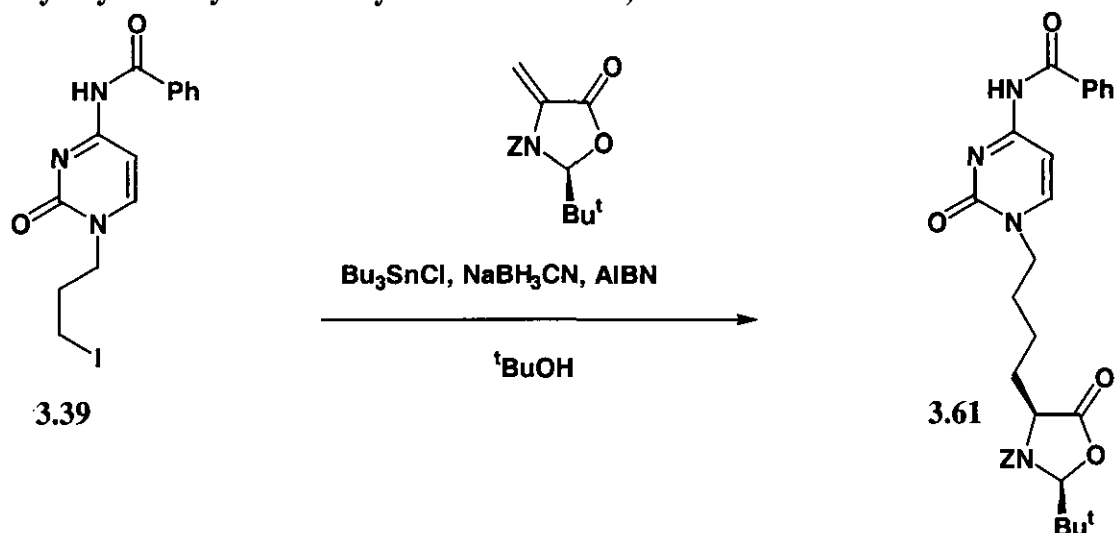
An experiment following method C, using *N*3-benzoyl-*N*1-(3-iodopropyl)uracil **3.33** (0.43 g, 1.12 mmol), AIBN (*ca.* 10 mg), toluene (150 ml) and tributyltin hydride (0.361 cm³, 0.391 g, 1.34 mmol), but without using the chiral acceptor **3.23**, gave the *title compound* **3.59** as a colourless oil (152 mg, 53%), having spectral data as above. No reduced *N*3-benzoyl-*N*1-propyluracil was observed.

*N*1-(2-Bromoethyl)thymine, **3.60**



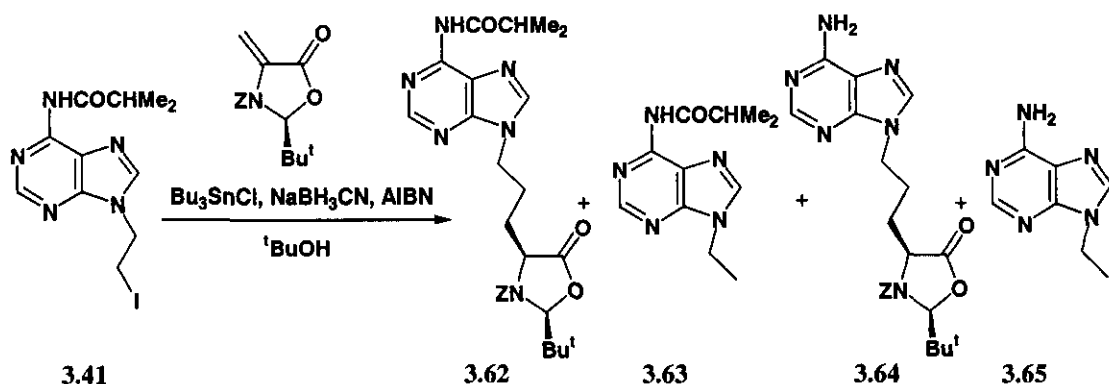
*N*3-Benzoyl-*N*1-(2-bromoethyl)uracil **3.25** (0.5 g, 1.41 mmol) and sodium cyanoborohydride (0.2 g, 2.82 mmol) were heated at reflux in *tert*-butanol (20 ml) for 40h. The solvent was removed in *vacuo* and the crude product was extracted with ethyl acetate (2 × 20 ml), washed with brine and dried over MgSO₄. The solvent was removed to yield only the title compound¹⁰⁷ **3.60** as a white solid (0.31 g, 94%), m.p. 166-167°C (lit.¹⁰⁷ 164-165°C). δ_{H} 1.96 (3H, d, *J* 1.2, CH₃), 4.30 (2H, t, *J* 8.5, CH₂Br), 4.75 (2H, t, *J* 8.5, NCH₂), 7.55 (1H, d, *J* 1.2, CH), 9.90 (1H, broad s, NH).

Attempted preparation of (2*S*,4*S*)-4-[*N*4-(4-benzoyl-1-cytosinyl)butyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one, 3.61



This was attempted following method D using *N*1-iodopropyl-*N*4-benzoylcytosine 3.39 (3.14 g, 8.20 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-*N*4-methyleneoxazolidin-5-one 3.23 (4.74 g, 16.4 mmol), tributyltin chloride (0.667 ml, 801 mg, 2.46 mmol), sodium cyanoborohydride (1.03 g, 16.4 mmol) and AIBN (0.8 mmol) heated at reflux in *tert*-butanol over 16 h. Purification of the residue by flash chromatography was attempted. A mixture of the *title compound* 3.61, the reduced starting *N*1-propyl-*N*4-benzoylcytosine and unknown products was isolated and could not be purified further. This mixture was therefore used directly in the next step.

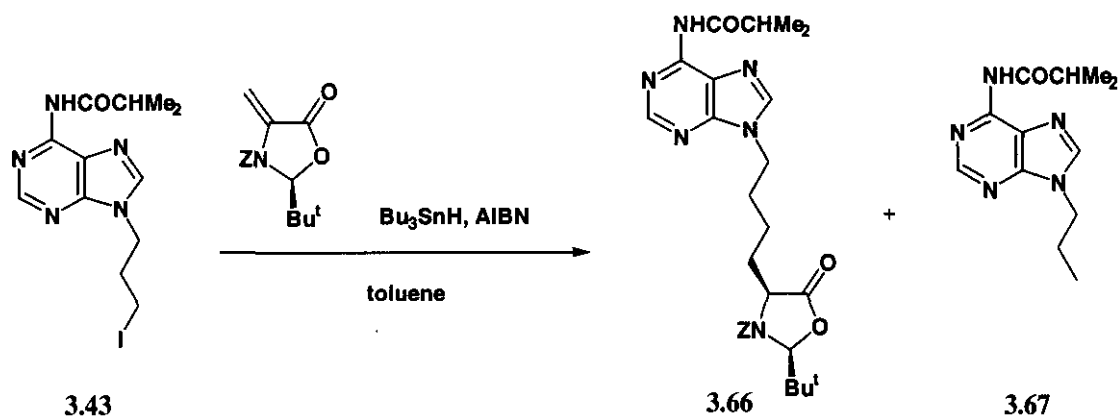
(2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-{3-[*N*6-(2-methylpropanoyl)-9-adeninyl]propyl}oxazolidin-5-one, 3.62, and (2*S*,4*S*)-4-[3-(9-adeninyl)propyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one, 3.64



Prepared following method D, using *N*9-(2-iodoethyl)-*N*6-(2-methylpropanoyl)adenine **3.41** (3.29 g, 9.16 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (5.30 g, 18.3 mmol), tributyltin chloride (0.746 cm³, 895 mg, 2.75 mmol), sodium cyanoborohydride (1.15 g, 18.3 mmol) and AIBN (0.92 mmol) but heated at reflux for 16 h to yield the *conjugate adduct* **3.62** as a colourless oil (1.17 g, 26%), a mixture of *deacylated conjugate adduct* **3.64** (580 mg, 14%, calculated from the following hydrolysis step) and *N*9-ethyl-*N*6-(2-methylpropionyl)adenine **3.63** (360 mg, 17%, calculated from the hydrolysis step), and *N*9-ethyladenine **3.65** (280 mg, 19%) as a white solid, m.p. 180-182°C (lit.¹¹⁰ 184-186°C). (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-{3-[*N*6-(2-methylpropanoyl)-9-adeninyl]propyl}oxazolidin-5-one **3.62**: Found: MH⁺ 523.2670. C₂₇H₃₄N₆O₅ requires: MH 523.2669; δ_H 0.91 (9H, s, CMe₃), 1.33 (6H, d, *J* 7.0, CHMe₂), 1.87-2.24 (4H, m, CHCH₂CH₂), 3.28 (1H, septet, *J* 7.0, CHMe₂), 4.27-4.34 (3H, m, CHCH₂ and NCH₂), 5.15 (2H, s, CH₂Ph), 5.52 (1H, s, CHBu^t), 7.26 (5H, m, ArH), 8.12 and 8.71 (each 1H, s, adenine-H), 9.74 (1H, s, NH); δ_C 19.0 (CHMe₂), 24.6 (CMe₃), 26.7 (CHCH₂CH₂), 29.0 (CHCH₂), 33.85 (CHMe₂), 35.8 (CMe₃), 43.2 (NCH₂), 56.5 (CHCH₂), 68.6 (CH₂Ph), 96.5 (CHBu^t), 122.0 (ArC), 128.5, 128.65 and 128.7 (ArCH), 134.9 (ArC), 143.0 (ArCH), 149.55 and 151.7 (ArC), 152.4 (ArCH), 156.1, 172.25 and 176.8 (CO); *m/z* 522 (M⁺, 2%), 395 (2), 359 (25) and 91 (100). (2*S*,4*S*)-4-[3-(9-Adeninyl)propyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one **3.64** (data from the mixture of **3.64** and **3.63**): δ_H 0.91 (9H, s, CMe₃), 1.79-2.25 (4H, m, CHCH₂CH₂), 4.22 (2H, t, *J* 7.0, NCH₂), 4.36 (1H, m, CHCH₂), 5.15 (2H, s, CH₂Ph), 5.56 (1H, s, CHBu^t), 7.26-7.38 (5H, m, ArH), 7.83 and 8.36 (each 1H, s, adenine-H). *N*9-Ethyl-*N*6-(2-methylpropanoyl)adenine **3.63** (data from the mixture of **3.65** and **3.63**): δ_H (CD₃OD) 1.26 (6H, d, *J* 7.0, CHMe₂), 1.51 (3H, t, *J* 7.3, CH₂CH₃) 2.91 (1H, septet, *J* 7.0, CHMe₂) and 4.31 (2H, q, *J* 7.3, CH₂CH₃), 8.37 and 8.63 (each 1H, s, 2-CH and 8-CH); δ_C (CD₃OD) 15.6 and 19.7 (CH₃), 37.1 (CHMe₂), 40.3 (CH₂CH₃), 127.05 (ArC), 145.3 (C-2 or C-8), 150.6 (ArC), 152.9 (C-8 or C-2), 153.2 (ArC) and 178.23 (CO). *N*9-Ethyladenine¹¹⁰ **3.65**: Found: M (EI) 163.0857. C₇H₉N₅ requires: M 163.0858; ν_{max}(KBr/cm⁻¹) 3268, 3191, 1675, 1601, 1573, 1480, 1415, 1327, 1308, 1249, 1214 and 1197; δ_H 1.62 (3H, t, *J* 7.3, CH₂CH₃), 4.26 (2H, q, *J* 7.3, CH₂CH₃), 6.09 (2H, s, NH), 7.86 and 8.37 (each 1H, s, 2-CH and 8-CH); δ_C (CD₃OD)

15.55 (CH₃), 38.9 (CH₂), 121.0 (ArC), 140.0 (C-2 or C-8), 150.4 (ArC), 152.8 (C-8 or C-2) and 155.5 (ArC); *m/z* 163 (M⁺, 60%), 135 (100) and 108 (70).

(2*S*,4*S*)-3-Benzoyloxycarbonyl-2-*tert*-butyl-4-{4-[*N*6-(2-methylpropanoyl)-9-adeninyl]butyl}oxazolidin-5-one, 3.66

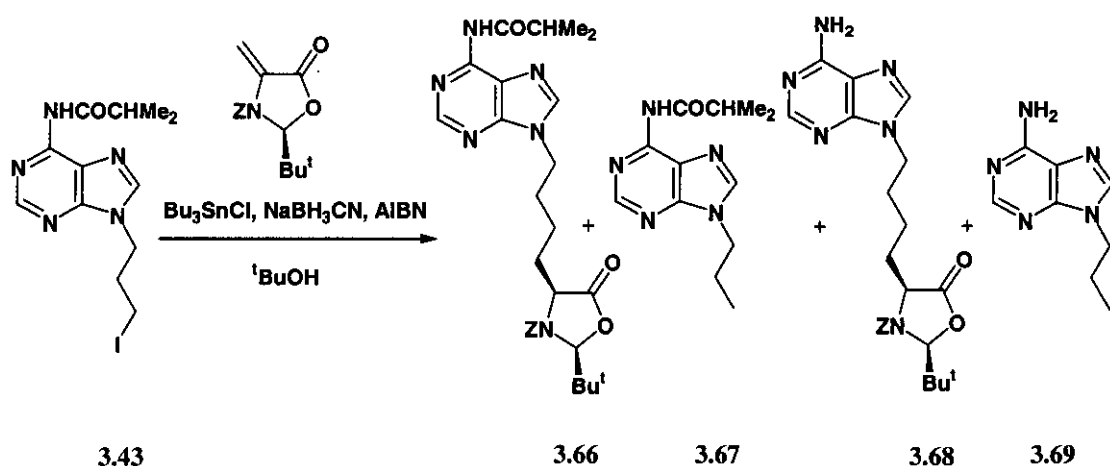


Prepared following method C, using *N*9-(3-iodopropyl)-*N*6-(2-methylpropanoyl)adenine **3.43** (0.31 g, 8.31 mmol), (2*S*,4*S*)-3-benzoyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (240 mg, 8.31 mmol), AIBN (*ca.* 10mg) and tributyltin hydride (0.268 ml, 0.290 g, 9.97 mmol) to give the *conjugate adduct* **3.66** as a colourless oil (102 mg, 23%) and *N*6-(2-methylpropanoyl)-*N*9-propyladenine **3.67** as a white gum (92.4 mg, 45%).

(2*S*,4*S*)-3-Benzoyloxycarbonyl-2-*tert*-butyl-4-{4-[*N*6-(2-methylpropanoyl)-9-adeninyl]butyl}oxazolidin-5-one **3.66**: Found: MH^+ 537.2811. $\text{C}_{28}\text{H}_{36}\text{N}_6\text{O}_5$ requires: MH 537.2747; $\nu_{\text{max}}(\text{KBr}/\text{cm}^{-1})$ 3343, 3055, 2975, 2875, 2359, 1790, 1718, 1615, 1586, 1462, 1402, 1372, 1349 and 1267; δ_{H} 0.94 (9H, s, CMe_3), 1.31 (6H, d, J 6.9, CHMe_2), 1.52-2.03 (6H, m, $\text{CHCH}_2\text{CH}_2\text{CH}_2$), 3.22 (1H, septet, J 6.9, CHMe_2), 4.18-4.26 (3H, m, CHCH_2 and NCH_2), 5.15 (2H, s, CH_2Ph), 5.54 (1H, s, CHBu^t), 7.29-7.39 (5H, m, ArH), 7.92 and 8.55 (each 1H, s, 2-CH and 8-CH) and 8.72 (1H, s, CONH); δ_{C} (CD_3OD) 19.7 (CHMe_2), 24.4 (CHCH_2CH_2), 25.6 (CMe_3), 30.2 ($\text{CHCH}_2\text{CH}_2\text{CH}_2$), 33.65 (CHCH_2), 37.15 (CHMe_2), 37.8 (CMe_3), 44.75 (NCH_2), 58.1 (CHCH_2), 69.3 (CH_2Ph), 97.7 (CHBu^t), 129.5, 129.6 and 129.9 (ArCH), 137.0 (ArC), 143.0 (ArCH), 149.8 and 150.7 (ArC), 153.1 (ArCH), 153.4 (ArC), 157.8, 174.55 and 176.25 (CO); *m/z* 537 (MH^+ , 100%), 515 (6), 379 (15), 260 (16), 202 (16) and 148 (25). *N*6-(2-Methylpropanoyl)-*N*9-propyladenine **3.67**: Found: MH^+ 248.1511. $\text{C}_{12}\text{H}_{17}\text{N}_5\text{O}$ requires: MH 248.1516; δ_{H} (CD_3OD) 0.94 (3H, t, J 7.2, CH_2CH_3),

1.38 (6H, d, J 6.9, CHMe_2), 1.88 (2H, sextet, J 7.2, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.31 (1H, septet, J 6.9, CHMe_2), 4.29 (2H, t, J 7.2, NCH_2CH_2), 8.38 and 8.62 (each 1H, s, 2-CH and 8-CH); δ_{C} (CD_3OD) 11.3 (CH_2CH_3), 19.65 (CHMe_2), 24.2 (CH_2CH_3), 37.1 (CHMe_2), 46.7 (NCH_2), 124.0 (ArC), 145.75 (ArCH), 150.65 (ArC), 152.9 (ArCH), 153.4 (ArC) and 178.2 (CO); m/z 247 (M^+ , 50%), 177 (60), 149 (58), 138 (100), 108 (30) and 84 (30).

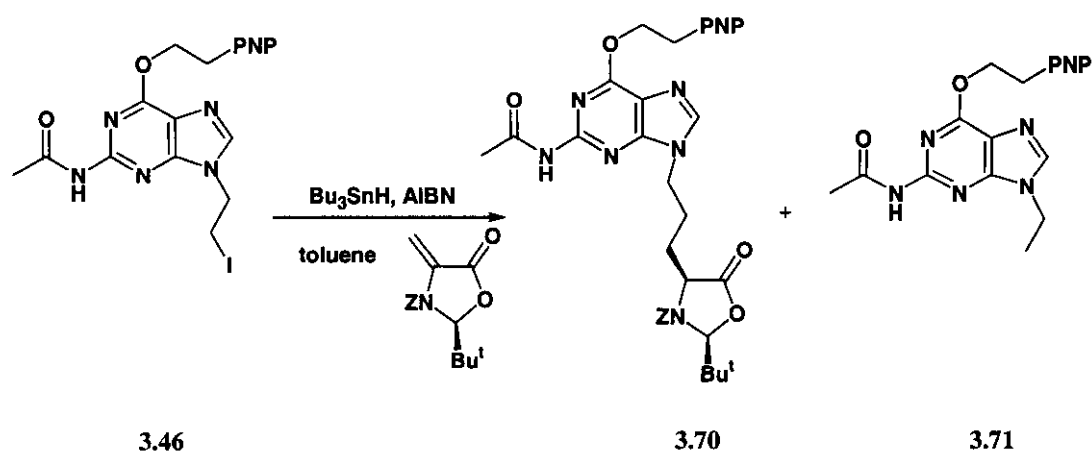
(2*S*,4*S*)-3-Benzoyloxycarbonyl-2-*tert*-butyl-4-{4-[*N*6-(2-methylpropanoyl)-9-adeninyl]butyl}oxazolidin-5-one, 3.66 and (2*S*,4*S*)-4-[4-(9-Adeninyl)butyl]-3-benzoyloxycarbonyl-2-*tert*-butyloxazolidin-5-one, 3.68



Prepared following method D, using *N*9-(3-iodopropyl)-*N*6-(2-methylpropanoyl)adenine **3.43** (1.86 g, 4.99 mmol), (2*S*)-3-benzoyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (2.88 g, 9.97 mmol), tributyltin chloride (0.406 cm³, 487 mg, 1.50 mmol), sodium cyanoborohydride (627 mg, 9.97 mmol) and AIBN (0.5 mmol) but heated at reflux for 16 h to yield the conjugate adduct **3.66** as a colourless oil (0.31 g, 12%), *deacylated conjugate adduct* **3.68** as a colourless oil (0.22 g, 14%), *N*6-(2-methylpropanoyl)-*N*9-propyladenine **3.67** as a white gum (0.13 g, 11%) and *N*9-propyladenine **3.69** also as a white gum (0.2 g, 23%). Data for (2*S*,4*S*)-3-benzoyloxycarbonyl-2-*tert*-butyl-4-{4-[*N*6-(2-methylpropionyl)-*N*9-adeninyl]butyl}oxazolidin-5-one **3.66** and for *N*6-(2-methylpropionyl)-*N*9-propyladenine **3.67** were identical to those given above. (2*S*,4*S*)-4-[4-(*N*9-Adeninyl)butyl]-3-benzoyloxycarbonyl-2-*tert*-butyloxazolidin-5-one **3.68**: Found: MH^+ (ES^+) 467.2401. $\text{C}_{24}\text{H}_{30}\text{N}_6\text{O}_4$ requires: MH 467.2407; $\nu_{\text{max}}(\text{KBr}/\text{cm}^{-1})$ 3323, 3300, 2874, 1790, 1718, 1645, 1600, 1481, 1396, 1348 and 1082; δ_{H} (CD_3OD) 0.91 (9H, s,

CMe_3), 1.35-2.22 (6H, m, $\text{CHCH}_2\text{CH}_2\text{CH}_2$), 4.15 (2H, t, J 7.0, NCH_2), 4.32 (1H, t, J 7.0, CHCH_2), 5.10 (2H, s, CH_2Ph), 5.54 (1H, s, CHBu^t), 7.24-7.35 (5H, m, ArH), 8.04 and 8.19 (each 1H, s, adenine-H); δ_{C} (CD_3OD) 24.4 (CHCH_2CH_2), 25.4 (CMe_3), 30.4 ($\text{CHCH}_2\text{CH}_2\text{CH}_2$), 33.7 (CHCH_2), 37.8 (CMe_3), 44.6 (NCH_2), 58.15 (CHCH_2), 69.3 (CH_2Ph), 97.7 (CHBu^t), 120.1 (ArC), 129.5, 129.6 and 129.9 (ArCH), 137.0 (ArC), 142.7 (ArCH), 150.7 (ArC), 153.7 (ArCH), 157.3 (ArC), 157.8 and 174.55 (CO); m/z 466 (M^+ , 80%), 409 (100), 365 (40) and 287 (70). *N*9-Propyladenine **3.69**: Found: MH^+ (ES^+) 178.1091. $\text{C}_8\text{H}_{11}\text{N}_5$ requires: MH 178.1092; ν_{max} (film/ cm^{-1}) 3408, 3055, 2985, 2361, 1636, 1474, 1418, 1327, 1266 and 896; δ_{H} 0.94 (3H, t, J 7.2, CH_2CH_3), 1.90 (2H, sextet, J 7.2, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.20 (2H, t, J 7.2, NCH_2), 6.23 (2H, s, NH_2), 7.82 and 8.35 (each 1H, s, 2-CH and 8-CH); δ_{C} (CD_3OD) 11.2 (CH_2CH_3), 22.8 (CH_2CH_3), 46.6 (NCH_2), 119.6 (ArC), 140.45 (ArCH), 150.1 (ArC), 152.9 (ArCH) and 155.7 (ArC); m/z 177 (M^+ , 55%), 148 (88), 135 (100) and 108 (60).

(2*S*,4*S*)-4-(3-{*N*2-Acetyl-*O*6-[2-(4-nitrophenyl)ethyl]-*N*9-guaninyl}propyl)-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one, 3.70



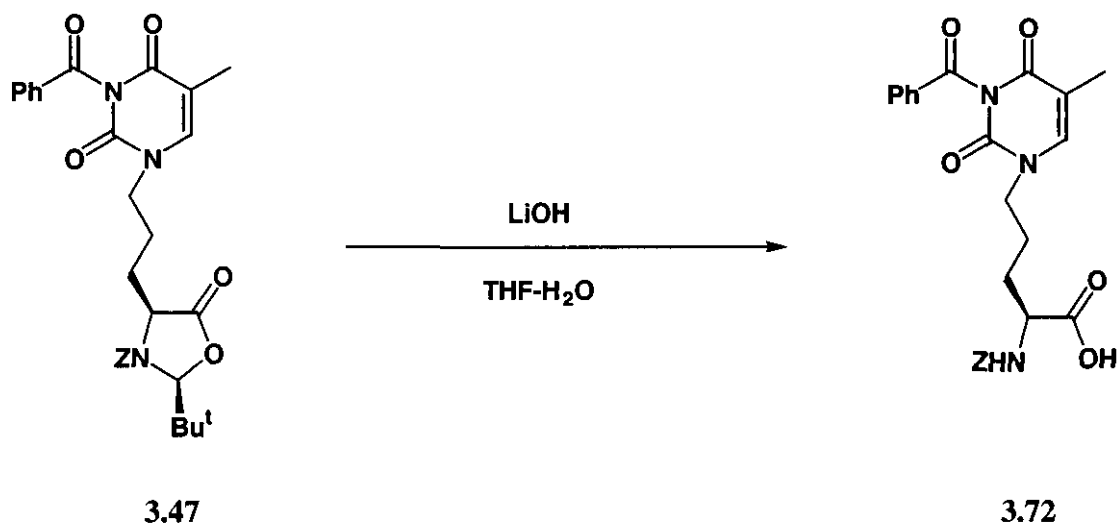
This was prepared following method C, using *N*2-acetyl-*N*9-(2-iodoethyl)-*O*6-[2-(4-nitrophenyl)ethyl]guanine **3.46** (1.0 g, 2.02 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **3.23** (587 mg, 2.02 mmol), AIBN (*ca.* 10mg) and tributyltin hydride (0.651 cm^3 , 0.704 g, 2.42 mmol) in toluene (200 cm^3) to give the *conjugate adduct* **3.70** as a yellow oil (279 mg, 21%) and *N*2-acetyl-9-ethyl-*O*6-[2-(4-nitrophenyl)ethyl]guanine **3.71** as a white solid (149 mg, 20%) m.p. (decomp.) 194-196°C). (2*S*,4*S*)-4-(3-{*N*2-Acetyl-*O*6-[2-(4-nitrophenyl)ethyl]-*N*9-guaninyl}propyl)-3-

benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one **3.70**: Found: MH^+ (CI) 660.2787. $C_{33}H_{37}N_7O_8$ requires: MH 660.2782; δ_H 0.91 (9 H, s, CMe_3), 1.72-2.13 (4 H, m, $CHCH_2CH_2$), 2.53 (3H, s, CH_3CO), 3.32 (2H, t, J 6.7, CH_2Ar), 4.18 (2H, m, NCH_2), 4.37 (1H, t, J 7.5, $CHCH_2$), 4.79 (2H, t, J 6.7, OCH_2), 5.16 (2H, s, CH_2Ph), 5.56 (1H, s, $CHBu^t$), 7.29-7.35 (5H, m, ArH), 7.50 (2H, d, J 8.6, ArH), 7.77 (1H, s, guanine-H), 7.85 (1H, s, CONH) and 8.19 (1H, d, J 8.62 Hz, ArH); δ_C 24.9 (CMe_3), 25.2 ($COCH_3$), 26.6 ($CHCH_2CH_2$), 30.05 ($CHCH_2$), 35.1 (CH_2), 36.9 (CMe_3), 43.1 (NCH_2), 56.5 ($CHCH_2$), 66.9 (CH_2), 68.7 (CH_2Ph), 96.5 ($CHBu^t$), 117.75 (ArC), 123.8, 128.6, 128.7 and 128.8 (ArCH) 128.9 (ArC), 130.0 (ArCH), 134.9 (ArC), 141.6 (ArCH), 145.7, 146.9, 152.0 and 153.15 (ArC), 156.1, 160.6 and 172.25 (CO); m/z 660 (MH^+ , 20%), 602 (100), 511 (60), 480 (40), 410 (40), 368 (30), 261 (70) and 193 (80). *N*2-Acetyl-*N*9-ethyl-*O*6-[2-(4-nitrophenyl)ethyl]guanine **3.71**: Found: M^+ (EI) 370.1390. $C_{17}H_{18}N_6O_4$ requires: M 370.1390; $\nu_{max}(KBr/cm^{-1})$; δ_H 3.60 (3H, t, J 7.3, CH_2CH_3), 2.53 (3H, s, CH_3CO), 3.31 (2H, t, J 6.6, CH_2Ar), 4.22 (2H, q, J 7.3, CH_2CH_3), 4.78 (2H, t, J 6.6, OCH_2), 7.50 (2H, d, J 8.6, ArH), 7.82 (1H, s, guanine-H), 7.87 (1H, s, CONH) and 8.18 (2H, d, J 8.56, ArH); m/z 370 (MH^+ , 100%), 341 (20), 328 (70), 277 (50), 262 (40) and 234 (84).

General procedure for conversion of 4-substituted oxazolidinones into *N*-benzyloxycarbonyl-(*S*)-amino acids by base hydrolysis (method E)

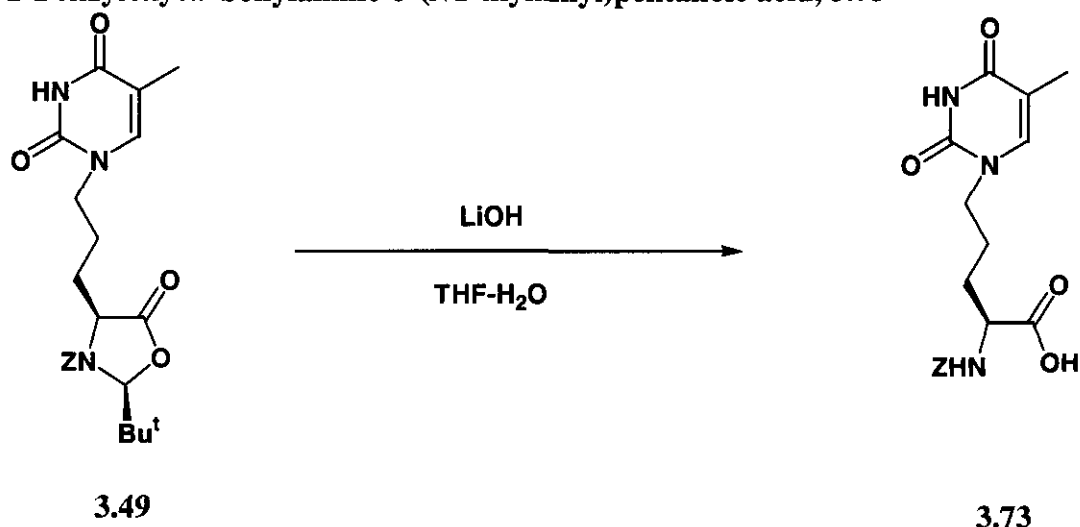
The oxazolidinone conjugate adduct in THF–water (3:1 v/v, 40 cm³) was cooled in an ice-bath and treated with lithium hydroxide monohydrate (2 mol equiv.). After stirring for 1 h at 0°C, water (50 cm³) was added and the THF removed under reduced pressure. The solution was acidified to pH 2-3 by careful addition of 1M hydrochloric acid, and the mixture was extracted with ethyl acetate (3 x 50 cm³). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give the (*S*)-amino acids.

(S)-5-(N3-benzoyl-N1-thyminyl)-2-benzyloxycarbonylaminopentanoic acid, 3.72



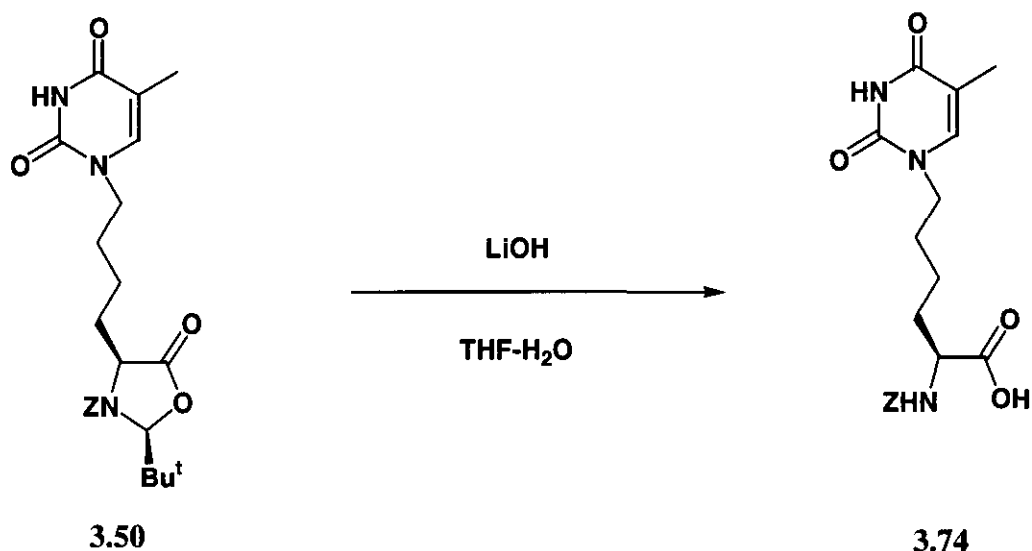
Prepared following method E, using (2*S*,4*S*)-4-[3-(*N*3-Benzoyl-*N*1-thyminyl)propyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one **3.47** (210 mg, 0.384 mmol) and lithium hydroxide monohydrate (0.768 mmol, 32 mg) to yield the *title compound* **3.72** (0.170 g, 92%) as a thick colourless oil that was incompletely characterized; $[\alpha]_{\text{D}}^{25} -13.3$ (*c*, 0.24 in EtOH); ν_{max} (film/ cm^{-1}) 3436, 3057, 2987, 2686, 2306, 2096, 1654, 1511, 1439, 1345, 1266, 1179, 896, 740; δ_{H} 1.62-1.96 (7H, m, CHCH_2CH_2 and $\text{CH}=\text{CCH}_3$), 3.65-3.74 (2H, t, *J* 6.6, NCH_2), 4.20 (1H, m, NHCHCH_2), 5.10 (2H, s, CH_2Ph), 5.58 (1H, d, *J* 7.9, NHCHCH_2), 7.09 (1 H, s, $\text{CH}=\text{CCH}_3$), 7.30-7.34 (5H, m, ArH), 7.44 (2H, m, ArH), 7.61 (1H, m, ArH), 7.87 (2H, m, ArH); δ_{C} 12.3 ($\text{CH}=\text{CCH}_3$), 24.8 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 29.2 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 48.1 (CH_2N), 53.0 (CHCH_2), 67.2 (CH_2Ph), 110.0 ($\text{CH}=\text{CCH}_3$), 125.3, 128.1, 128.2, 128.6, 129.0 and 129.2 (ArCH), 130.4 and 135.15 (ArC), 140.4 ($\text{CH}=\text{CCH}_3$), 150.0, 156.3, 163.3, 169.1 and 175.0 (CO).

(S)-2-Benzylloxycarbonylamino-5-(N1-thyminy)pentanoic acid, 3.73



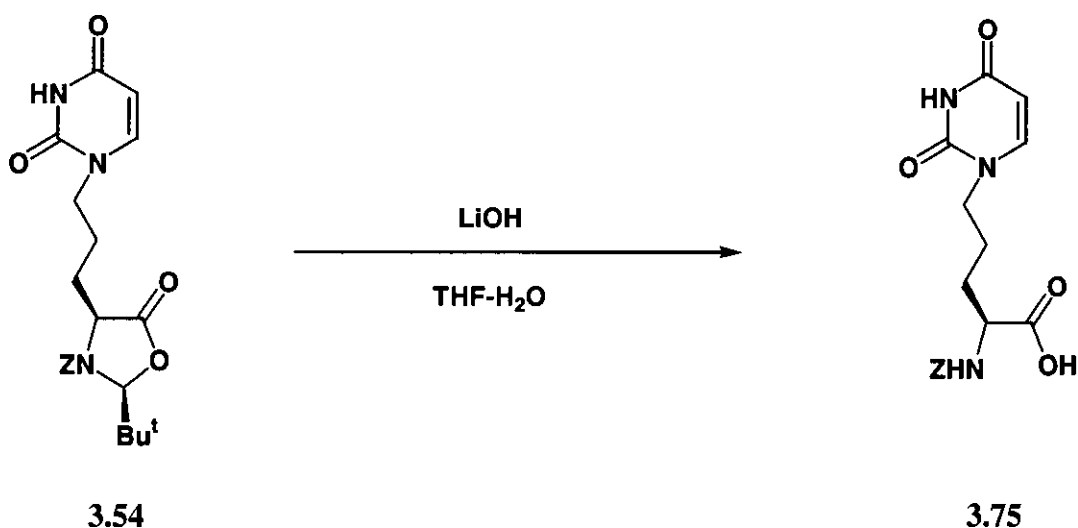
Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-4-[3-(*N*1-thyminy)propyl]-2-*tert*-butyloxazolidin-5-one **3.49** (210 mg, 0.474 mmol) and lithium hydroxide monohydrate (0.948 mmol, 40 mg) to yield the *title compound* **3.73** (0.170 g, 96%) as a white amorphous solid, m.p. (decomp.) 199-100°C; $[\alpha]_{\text{D}}^{25}$ -11.3 (*c*, 0.32 in EtOH); Found: MNH_4^+ (ES^+) 393.1777. $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_6$ requires: MNH_4 393.1774; $\nu_{\text{max}}(\text{KBr}/\text{cm}^{-1})$ 3306, 3191, 3062, 3035, 2959, 2827, 2602, 2366, 2345, 2252, 1654, 1531, 1358, 1217, 1133, 1066 and 910; δ_{H} 1.55-1.84 (7H, m, CHCH_2CH_2 and $\text{CH}=\text{C}(\text{CH}_3)$), 3.65-3.81 (2H, t, *J* 6.6, NCH_2), 4.27 (1H, m, NHCHCH_2), 5.02 (2H, s, CH_2Ph), 5.99 (1H, d, *J* 7.7, NHCHCH_2), 7.00 (1H, s, $\text{CH}=\text{CCH}_3$), 7.23-7.47 (5H, m, ArH), 10.25 (1H, s, CONH); δ_{C} 12.2 ($\text{CH}=\text{CCH}_3$), 21.1 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 29.2 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 48.0 (CH_2N), 53.2 (CHCH_2), 67.0 (CH_2Ph), 110.95 ($\text{CH}=\text{CCH}_3$), 128.0, 128.2 and 128.5 (ArCH), 136.2 (ArC), 141.0 ($\text{CH}=\text{CCH}_3$), 151.5, 165.2, 156.4 and 151.5 (CO); *m/z* 393 (MNH_4^+ , 100%), 376 (80), 349 (55), 332 (40) and 285 (70).

(S)-2-Benzylloxycarbonylamino-6-(N1-thyminy)hexanoic acid, 3.74



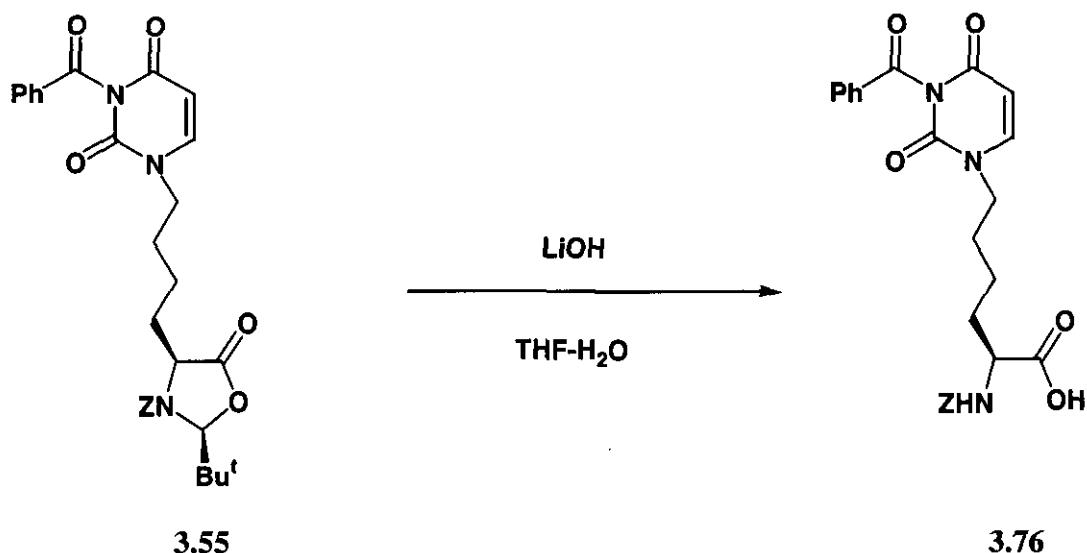
Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-4-[4-(1-thyminy)butyl]-2-*tert*-butylloxazolidin-5-one **3.50** (310 mg, 0.678 mmol) and lithium hydroxide monohydrate (85 mg, 2.04 mmol) to yield the *title compound* **3.74** as a thick colourless oil (230 mg, 87%); Found: MNH_4^+ 407.1940. $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_6$ requires: MNH_4 407.1931; $\nu_{\text{max}}(\text{film}/\text{cm}^{-1})$ 3430, 2959, 2348, 1657, 1546, 1501, 1467, 1129 and 1070; δ_{H} 1.21-1.88 (9H, m, $\text{CH}(\text{CH}_2)_3\text{CH}_2\text{N}$ and $\text{CH}=\text{CCH}_3$), 3.66 (2H, m, NCH_2), 4.37 (1H, m, CHCH_2), 5.79 (1H, d, J 7.9, NHCH), 6.98 (1H, s, $\text{CH}=\text{CCH}_3$), 7.26-7.37 (5H, m, ArH) and 10.17 (1H, s, CONH); δ_{C} 12.2 ($\text{CH}=\text{CCH}_3$), 21.7, 28.35 and 31.7 (CH_2), 48.0 (NCH_2), 53.4 (CHCH_2), 67.0 (CH_2Ph), 110.9 ($\text{CH}=\text{CCH}_3$), 128.0, 128.15 and 128.5 (ArCH), 136.3 (ArC), 140.9 ($\text{CH}=\text{CCH}_3$), 151.45, 156.2, 165.1 and 175.6 (CO); m/z 390 (M^+ , 75%), 363 (90), 346 (100), 299 (88) and 282 (80).

(S)-2-Benzylloxycarbonylamino-5-(N1-uracilyl)pentanoic acid, 3.75



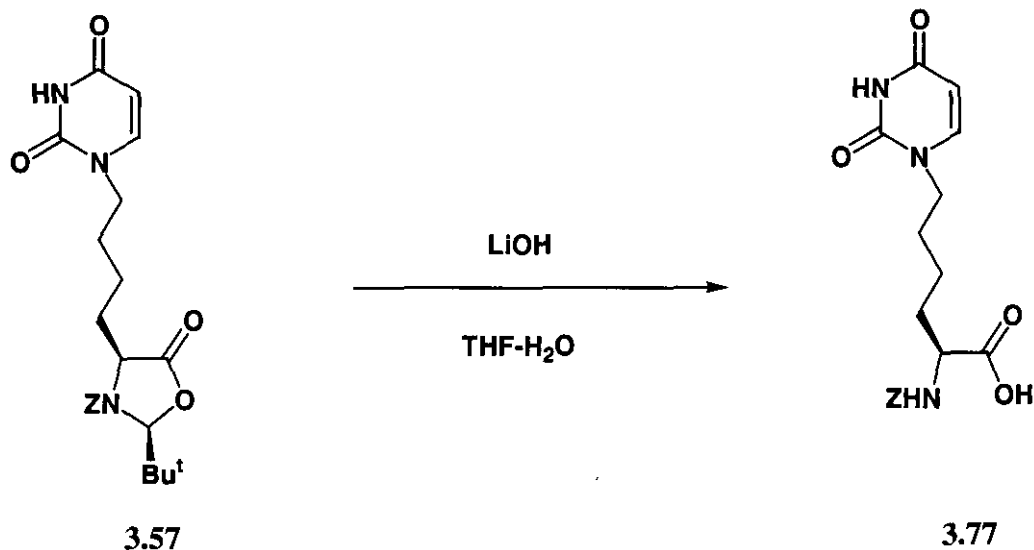
Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-4-[3-(*N*1-uracilyl)propyl]-2-*tert*-butylloxazolidin-5-one **3.54** (2.34 g, 5.45 mmol) and lithium hydroxide monohydrate (687 mg, 16.4 mmol) to yield the *title compound* **3.75** (1.35 g, 69%) as a thick oil; $[\alpha]_{\text{D}}^{25} -71.6$ (*c*, 0.10 in EtOH); Found: MH^+ 362.1352. $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_6$ requires: MH 362.1352; ν_{max} (film/ cm^{-1}) 3426, 3056, 2988, 2686, 2361, 2339, 2307, 2300, 2245, 2095, 1660 and 1266; δ_{H} (CD_3OD) 1.55-1.82 (4H, m, CHCH_2CH_2), 3.65 (2H, t, *J* 6.4, NCH_2), 4.11 (1H, m, CHCH_2), 4.98 (2H, s, CH_2Ph), 5.52 (1H, d, *J* 7.8, $\text{CH}=\text{CHCO}$), 7.17-7.26 (5H, m, ArH) and 7.51 (1H, d, *J* 7.8 Hz, $\text{CH}=\text{CHCO}$); δ_{C} (CD_3OD) 21.5 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 29.65 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 48.7 (CH_2N), 54.8 (CHCH_2), 67.6 (CH_2Ph), 102.3 ($\text{CH}=\text{CHCO}$), 128.8, 129.0 and 129.5 (ArCH), 138.2 (ArC), 147.15 ($\text{CH}=\text{CHCO}$), 152.8, 158.6, 166.7 and 175.4 (CO); *m/z* 361 (M^+ , 100%), 344 (40), 318 (55) and 296 (20).

(S)-6-(N3-Benzoyl-N1-uracilyl)-2-benzyloxycarbonylaminohexanoic acid, 3.76



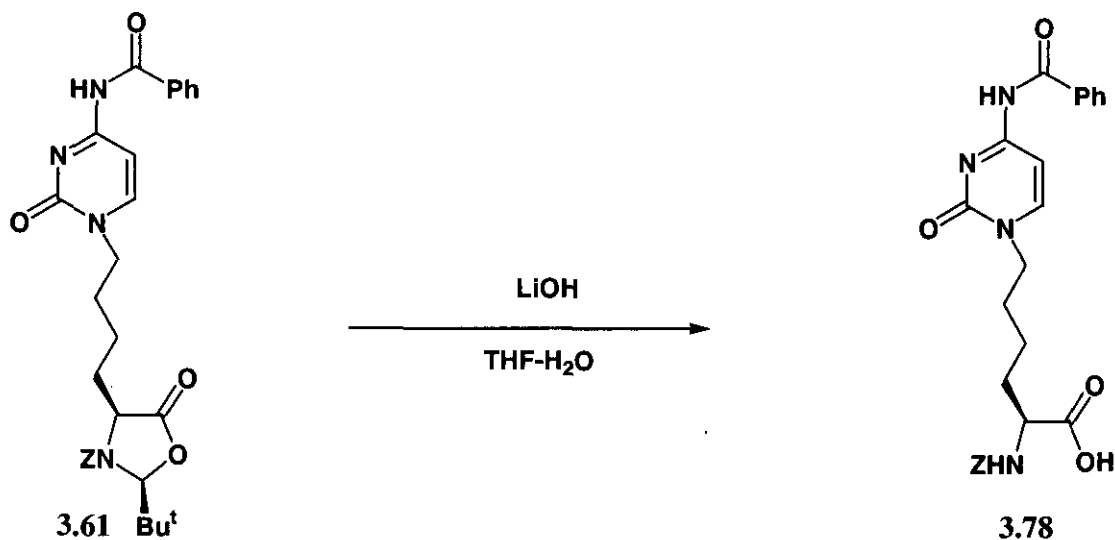
Prepared following method E, using (2*S*,4*S*)-4-[4-(3-benzoyl-1-uracilyl)butyl]3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one **3.55** (112.6 mg, 0.206 mmol) and lithium hydroxide monohydrate (17 mg, 0.412 mmol) to yield the *title compound* **3.76** as a thick colourless oil (95 mg, 96%); Found: MNH_4^+ 497.2038. $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_7$ requires: MNH_4 497.2036; $\nu_{\text{max}}(\text{KBr}/\text{cm}^{-1})$ 3436, 3057, 2989, 2686, 2306, 2096, 1654 and 1266; δ_{H} 1.23-2.04 (6H, m, $\text{CHCH}_2\text{CH}_2\text{CH}_2$), 3.66 (2H, m, NCH_2), 4.32 (1H, m, CHCH_2), 5.02 (2H, s, CH_2Ph), 5.59 and 6.98 (each 1H, d, J 8.0, $\text{CH}=\text{CHCO}$), 7.13-7.32 (5H, m, ArH), 7.46 (2H, m, ArH) 7.72 (1H, m, ArH) and 7.87 (2H, m, ArH); δ_{C} 21.8, 28.1 and 31.4 (CH_2), 48.6 (NCH_2), 53.3 (CHCH_2), 67.1 (CH_2Ph), 101.8 ($\text{CH}=\text{CHCO}$), 128.0, 128.2, 128.5, 129.2 and 130.3 (ArCH), 131.2 (ArC), 135.2 (ArCH), 136.0 (ArC), 144.6 ($\text{CH}=\text{CHCO}$), 149.7, 156.2, 162.8, 168.8 and 175.38 (CO). m/z 479 (M^+ , 15%), 374 (20), 153 (25) and 121 (100).

(S)-2-Benzyloxycarbonylamino-6-(N1-uracilyl)hexanoic acid, 3.77



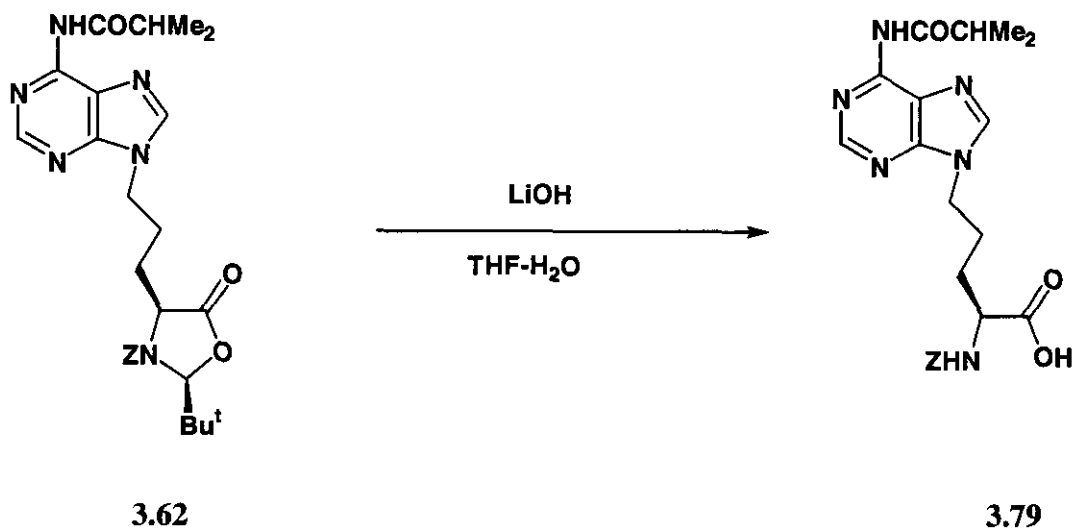
Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[4-(*N*1-uracilyl)butyl]oxazolidin-5-one **3.57** (250 mg, 0.564 mmol) and lithium hydroxide monohydrate (47 mg, 1.13 mmol) to yield the *title compound* **3.77** as a white solid (110 mg, 52%), m.p. (decomp.) 182-183°C; $[\alpha]_{\text{D}}^{25}$ -150 (*c*, 0.032 in EtOH); Found: MH^+ 376.1513. $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_6$ requires: MH 376.1508; $\nu_{\text{max}}(\text{KBr}/\text{cm}^{-1})$ 3213, 2364, 1715, 1688, 1541, 1466, 1364, 1257, 1200 and 1072; δ_{H} ($\text{DMSO}-d_6$) 1.15-1.56 (6H, m, CH $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.62 (2H, t, *J* 6.8, NCH_2), 3.89 (1H, m, CHCH_2), 5.02 (2H, s, CH_2Ph), 5.50 (1H, d, *J* 7.9, $\text{CH}=\text{CHCO}$), 7.31-7.34 (5H, m, ArH), 7.55 (1H, d, *J* 7.8, CHNH) 7.61 (1H, d, *J* 7.9, $\text{CH}=\text{CHCO}$) and 11.21 (1H, s, uracil-NH); δ_{C} 22.4, 27.9 and 30.3 (CH_2), 47.1 (NCH_2), 53.6 (CHCH_2), 65.3 (CH_2Ph), 100.7 ($\text{CH}=\text{CHCO}$), 127.6, 127.7 and 128.2 (ArCH), 136.9 (ArC), 145.55 ($\text{CH}=\text{CHCO}$), 150.8, 156.0, 163.6 and 173.7 (CO); m/z 376 (MH^+ , 80%), 332 (70), 285 (90), 268 (100), 244 (100) and 226 (50).

(S)-6-(N4-Benzoyl-N1-cytosinyl)-2-benzyloxycarbonylaminohexanoic acid, 3.78



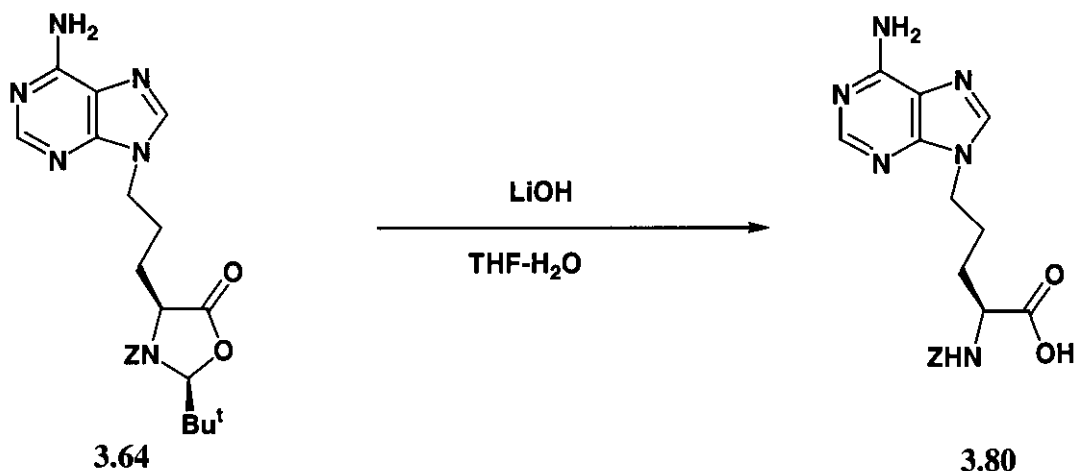
This was prepared following method E using crude (2S,4S)-4-[4-(N4-benzoyl-N1-cytosinyl)butyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one **3.61** to yield the crude *title compound* **3.78** which could not be purified despite several attempts using column chromatography ; Found (MH^+) 479.1932, $\text{C}_{25}\text{H}_{26}\text{N}_4\text{O}_6$ requires MH 479.1930; m/z 479 (MH^+ , 90%), 362 (100), 271 (80), 254 (82), 243 (100), 230 (90), 220 (98).

(S)-2-Benzyloxycarbonylamino-5-[N6-(2-methylpropanoyl)-N9-adeninyl]pentanoic acid, 3.79



Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-{3-[*N*6-(2-methylpropionyl)-*N*9-adeninyl]propyl}oxazolidin-5-one **3.62** (0.91 g, 1.74 mmol) and lithium hydroxide monohydrate (219 mg, 5.23 mmol) to yield the *title compound* **3.79** as a white amorphous solid (0.57 g, 72%), m.p. (decomp.) 147-150°C; Found: MH^+ 455.2043; $C_{22}H_{26}N_6O_5$ requires: MH 455.2052; δ_H 1.28 (6H, d, J 6.8, $CHMe_2$), 1.74-2.27 (4H, m, $CHCH_2CH_2$), 3.03 (1H, septet, J 6.8, $CHMe_2$), 4.36 (2H, m, NCH_2), 4.52 (1H, m, $CHCH_2$), 5.11 (2H, s, CH_2Ph), 5.73 (1H, d, J 7.5, $CHNH$), 7.33 (6H, m, $5 \times ArH$ and $NHCO$), 8.17 and 8.69 (each 1H, s, 2-CH and 8-CH); δ_C 19.2 ($CHMe_2$), 25.5 ($CHCH_2CH_2$), 28.6 ($CHCH_2$), 36.0 ($CHMe_2$), 43.4 (NCH_2), 53.5 ($CHCH_2$), 67.1 (CH_2Ph), 122.0 (ArC), 128.1, 128.3 and 128.6 (ArCH), 136.8 (ArC), 143.1 (ArCH), 149.3 and 151.6 (ArC), 152.9 (ArCH), 156.2, 172.8 and 176.5 (CO); m/z 455 (MH^+ , 70%), 347 (100), 277 (30), 206 (62) and 196 (70)

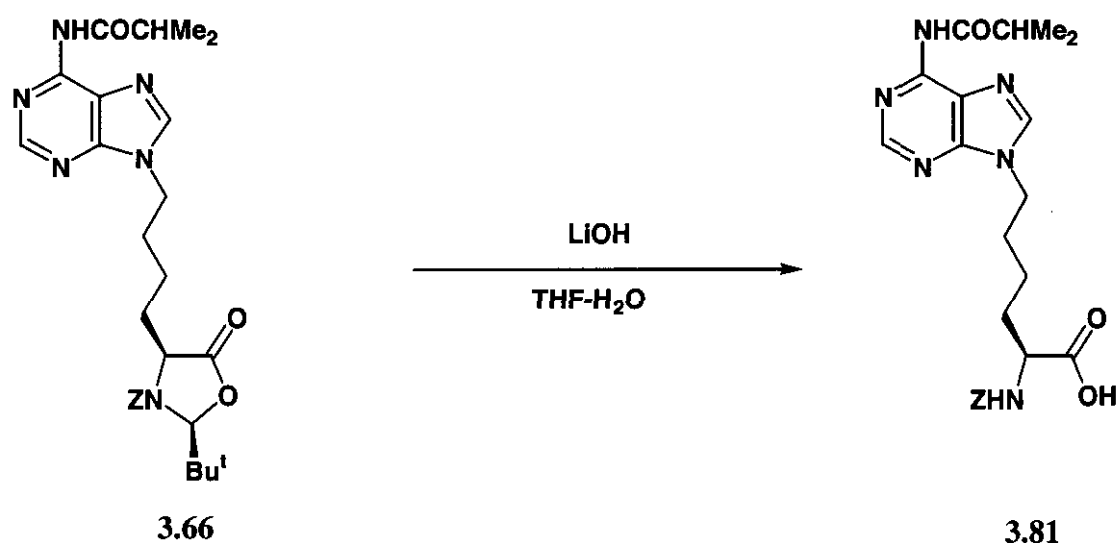
(*S*)-5-(*N*9-Adeninyl)2-benzyloxycarbonylaminopentanoic acid, **3.80**



Prepared following a modified method E, using a mixture of (2*S*,4*S*)-4-[3-(*N*9-adeninyl)propyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one **3.64** (580 mg, 1.28 mmol), *N*9-ethyl-*N*6-(2-methylpropionyl)adenine **3.63** (360 mg, 1.55 mmol) and lithium hydroxide monohydrate (162 mg, 3.85 mmol), and extracting with dichloromethane (3 x 20 cm³) to yield *N*9-ethyl-*N*6-(2-methylpropanoyl)adenine **3.63** (360 mg, 17% based on iodo compound **3.41**). Acidification and extraction of the aqueous layer as usual gave the *title compound* **3.80** as a white solid (430 mg, 87%), m.p. 193-94°C; Found: MH^+ (ES^+) 385.1629. $C_{18}H_{20}N_6O_4$ requires: MH 385.1624; $\nu_{max}(KBr/cm^{-1})$ 3395, 3104, 2876, 2366,

2346, 1970, 1611, 1542, 1459, 1408, 1323 and 1221; δ_{H} (CD_3OD) 1.61-2.05 (4H, m, CHCH_2CH_2), 4.22 (1H, m, CHCH_2), 4.43 (2H, m, NCH_2), 5.02 (2H, s, CH_2Ph), 7.23-7.31 (5H, m, ArH), 8.50 and 8.58 (each 1H, s, 2-CH and 8-CH); δ_{C} (CD_3OD) 27.4 and 29.4 (CH_2), 45.1 (NCH_2), 54.8 (CHCH_2), 67.6 (CH_2Ph), 119.8 (ArC), 128.6, 128.9 and 129.4 (ArCH), 138.0 (ArC), 145.1 and 145.7 (ArCH), 150.0 and 151.2 (ArC), 158.5 and 174.0 (CO); m/z 385 (MH^+ , 15%), 251 (5), 190 (46), 126 (70), 111 (100) and 84 (90).

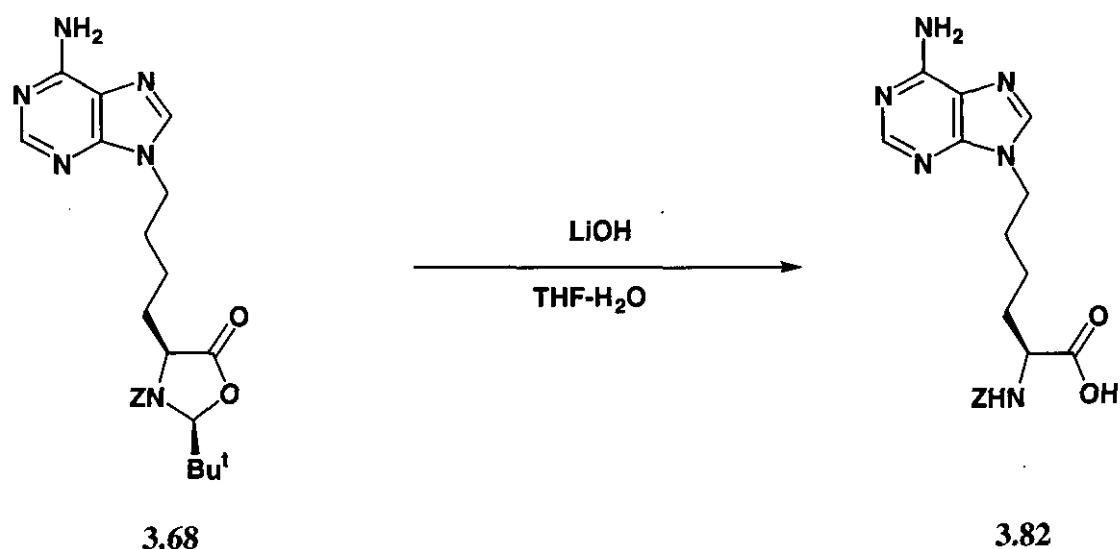
(S)-6-[N6-(2-Methylpropanoyl)-N9-adeninyl]-2-benzyloxycarbonylaminohexanoic acid, 3.81



Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-{4-[N6-(2-methylpropanoyl)-N9-adeninyl]butyl}oxazolidin-5-one **3.66** (0.32 g, 0.597 mmol) and lithium hydroxide monohydrate (84 mg, 0.199 mmol) to yield the *title compound* **3.81** as a white amorphous solid (0.250 g, 89%), m.p. 147-150°C; Found: MH^+ (ES^+) 469.2208; $\text{C}_{23}\text{H}_{28}\text{N}_6\text{O}_5$ requires: MH 469.2199; ν_{max} ($\text{KBr}/\text{cm}^{-1}$) 3322, 3054, 2974, 2556, 1723, 1683, 1609, 1590, 1540, 1457, 1402, 1350, 1072, 1050 and 968; δ_{H} (CD_3OD) 1.28 (6H, d, J 6.9, CHMe_2), 1.34-2.21 (6H, m, $\text{CHCH}_2\text{CH}_2\text{CH}_2$), 2.91 (1H, septet, J 6.9, CHMe_2), 4.14 (1H, m, CHCH_2), 4.31 (2H, t, J 7.0, NCH_2), 5.04 (2H, s, CH_2Ph), 7.26-7.32 (5H, m, ArH), 8.35 and 8.63 (each 1H, s, 2-CH and 8-CH); δ_{C} (CD_3OD) 19.2 (CHMe_2), 23.9, 28.9 and 32.11 (CH_2), 37.1 (CHMe_2), 44.8 (NCH_2), 53.73 (CHCH_2), 67.6 (CH_2Ph), 123.75 (ArC), 128.7, 128.9 and 129.4 (ArCH), 138.15 (ArC), 145.6 (ArCH), 150.5 (ArC), 152.9 (ArCH), 153.3

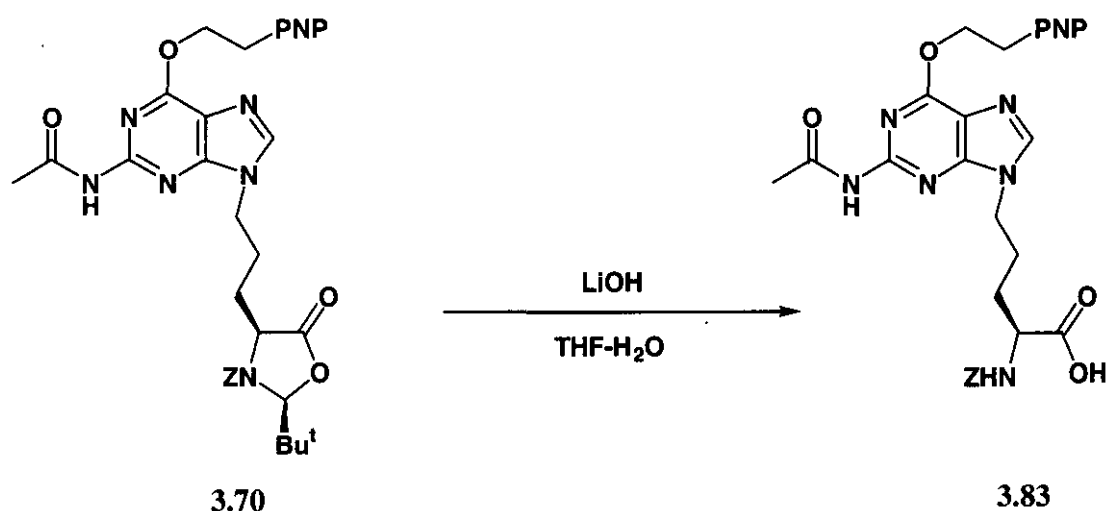
(ArC), 158.6, 175.7 and 178.2 (CO); m/z 469 (MH^+ , 100%), 399 (40), 361 (50), 335 (30) and 291 (42).

(S)-6-(N9-Adeniny)-2-benzyloxycarbonylaminohexanoic acid, 3.82



Prepared following method E, using (2S,4S)-4-[4-(N9-adeninyl)butyl]-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one **3.68** (0.27 g, 0.579 mmol) and lithium hydroxide monohydrate (73 mg, 1.74 mmol) to yield the *title compound* **3.82** as a white amorphous gum (0.197 g, 86%); Found: MH^+ (ES^+) 399.1778. $C_{19}H_{22}N_6O_4$ requires: MH 399.1781; $\nu_{\max}(\text{KBr}/\text{cm}^{-1})$ 3327, 2971, 2361, 2342, 1704, 1515, 1266 and 1202; δ_H (CD_3OD) 1.38-1.98 (6H, m, $CHCH_2CH_2CH_2$), 4.14 (1H, m, $CHCH_2$), 4.25 (2H, t, J 7.0, NCH_2), 5.06 (2H, s, CH_2Ph), 7.25-7.33 (5H, m, ArH), 8.18 and 8.26 (each 1H, s, 2-CH and 8-CH); δ_C (CD_3OD) 23.9 ($CHCH_2CH_2$), 30.45 ($CHCH_2CH_2CH_2$), 32.1 ($CHCH_2$), 44.9 (NCH_2), 55.0 ($CHCH_2$), 67.6 (CH_2Ph), 126.15, 128.8, 129.0 and 129.5 (ArCH), 138.2, 139.2 and 143.9 (ArC), 150.2 (ArCH), 155.0 (ArC), 158.6 and 176.15 (CO); m/z 399 (MH^+ , 100%), 355 (15), 291 (60), 265 (60) and 247 (40).

(S)-5-{N2-Acetyl-O6-[2-(4-nitrophenyl)ethyl]-N9-guaninyl}-2-benzyloxycarbonylaminopentanoic acid, 3.83



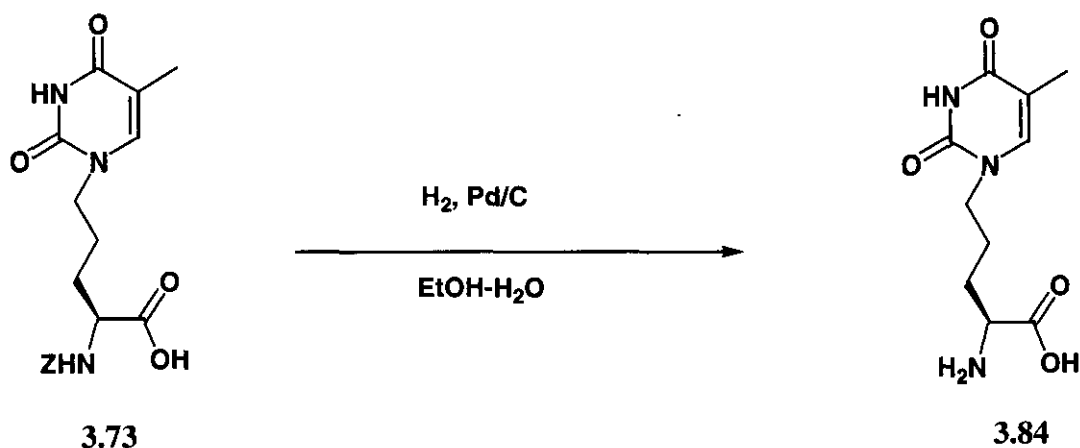
Prepared following method E, using (2*S*,4*S*)-4-(3-{*N*2-acetyl-*O*6-[2-(4-nitrophenyl)ethyl]-*N*9-guaninyl}propyl)-3-benzyloxycarbonyl-2-*tert*-butyloxazolidin-5-one **3.70** (60 mg, 0.091 mmol) and lithium hydroxide (10 mg, 0.18 mmol) to yield the *title compound* **3.83** as a yellow solid (47 mg, 87%), m.p. 143-144°C; Found: MH^+ 592.2156. $C_{28}H_{29}N_7O_8$ requires; MH 592.2154; $\nu_{max}(KBr/cm^{-1})$ 3466, 2961, 2363, 2345, 1719, 1687, 1664, 1610, 1518, 1345 and 1236; δ_H (DMSO- d_6) 1.45-1.85 (4H, m, $CHCH_2CH_2$), 2.20 (3H, s, CH_3CO), 3.35 (2H, t, J 6.7, CH_2Ar), 3.60 (1H, m, $CHCH_2$), 4.20 (2H, m, NCH_2), 4.75 (2H, t, J 6.7, OCH_2), 4.97 (2H, br s, CH_2Ph), 5.80 (1H, d, J 7.5, $CHNH$), 6.43 (1H, s, guanine-H), 7.20-7.40 (5H, m, ArH), 7.60 and 8.19 (each 2H, d, J 8.6, ArH) and 10.35 (1H, s, CONH); m/z 592 (MH^+ , 60%), 562 (40), 546 (38), 516 (100), 484 (40) and 428 (65). **3.83** was too insoluble in DMSO- d_6 for ^{13}C spectra analysis and interpretation.

General procedure for removal of a benzyloxycarbonyl group (Z) by hydrogenolysis to afford amino acids (method F)

The Z-protected amino acid (1 mol equiv.) in ethanol (140 cm^3) and water (60 cm^3) was degassed with a stream of argon for 15 min. Palladium-charcoal catalyst (10 mol%, 0.1 mol equiv.) was added and a stream of hydrogen was passed through the solution under vigorous stirring for 8h. The solution was again degassed with a stream of argon for 15 min, and the catalyst was filtered and washed with a small amount of ethanol and water.

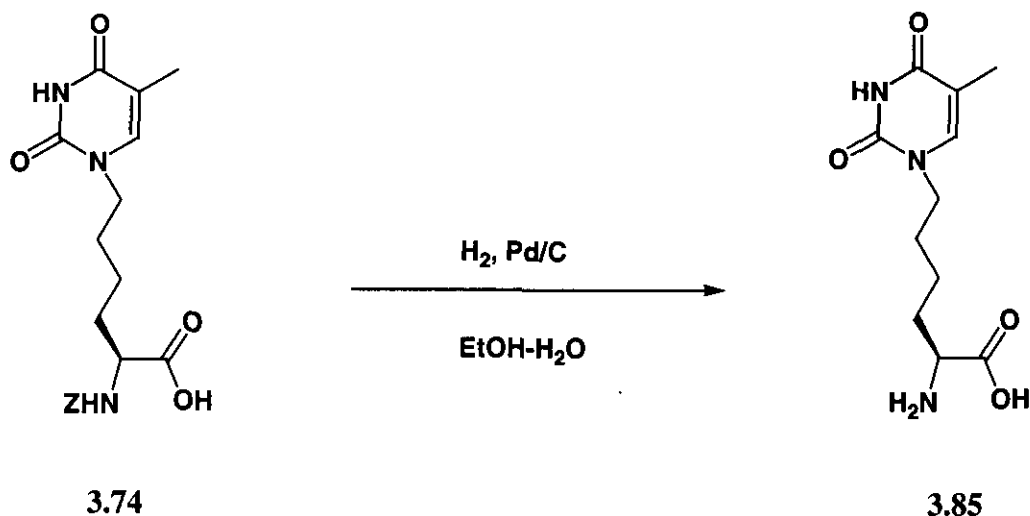
The solvents were removed under reduced pressure, toluene (20 cm³) was added and removed under reduced pressure (3 times) to eliminate traces of water. The crude residue was dried under vacuum to yield the free amino acid.

(S)-2-Amino-5-(N1-thyminy)pentanoic acid, 3.84



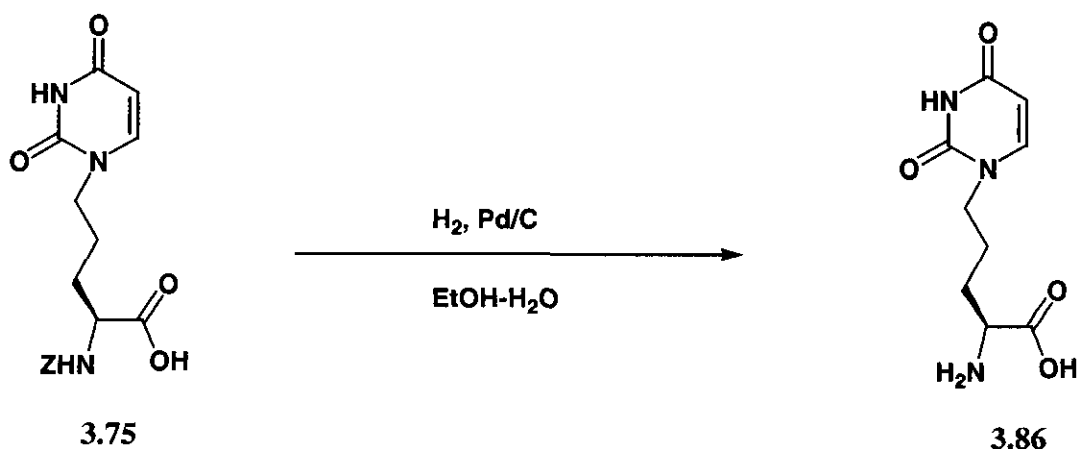
Prepared following method F, using (S)-2-benzyloxycarbonylamino-5-(N1-thyminy)pentanoic acid **3.73** (1.61 g, 4.29 mmol) and Pd/C (200 mg) to yield the *title compound* **3.84** as a white solid (760 mg, 74%), m.p. (decomp.) 124-125°C; Found: MH⁺ (ES⁺) 242.1144. C₁₀H₁₅N₃O₄ requires: MH 242.1141; ν_{max} (KBr/cm⁻¹) 3448, 3153, 3034, 2362, 1685, 1674, 1600, 1475, 1460, 1420 and 1220; δ_{H} (D₂O) 1.57-1.91 (7H, m, CHCH₂CH₂ and CH=CCH₃), 3.57-3.71 (2H, m, NCH₂), 3.85 (1H, t, *J* 5.5, CHCH₂) and 7.29 (1 H, s, CH=CCH₃); δ_{C} (D₂O) 11.7 (CH=CCH₃), 24.3 (CHCH₂CH₂), 27.2 (CHCH₂), 48.2 (CH₂N), 53.45 (CHCH₂), 111.3 (ArC), 143.4 (CH=CCH₃), 152.7, 167.3 and 173.1 (CO); *m/z* 242 (MH⁺, 50%), 198 (100), 169 (53), 146 (52), 127 (54), 113 (44) and 70 (70).

(S)-2-Amino-6-(N1-thyminy)hexanoic acid, 3.85



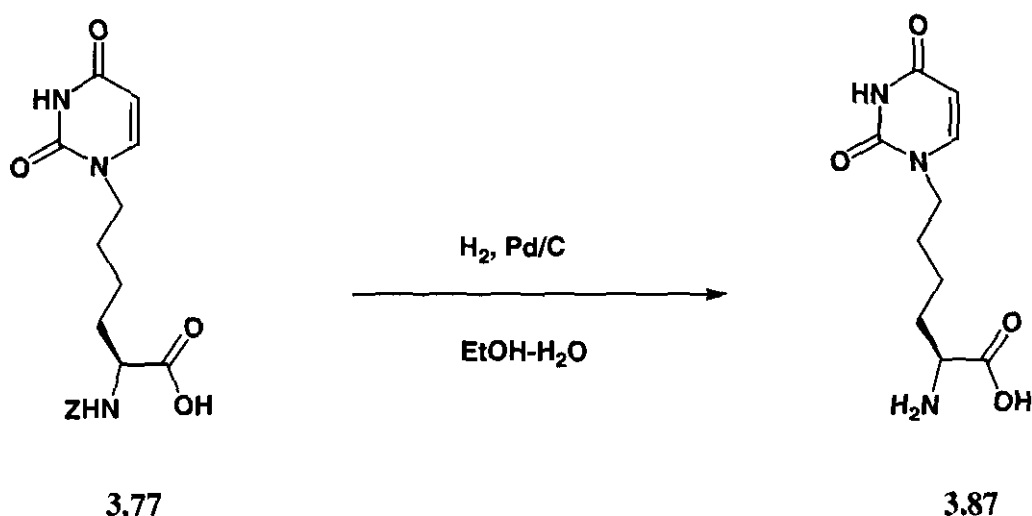
Prepared following method F, using (2S)-benzyloxycarbonylamino-6-(N1-thyminy)hexanoic acid **3.74** (1.32 g, 3.39 mmol) and Pd/C (300 mg) to yield the *title compound* **3.85** as a white solid (680 mg, 79%), m.p. 219-220°C; Found: MH^+ (ES^+) 256.1296. $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}_4$ requires: MH 256.1297; $\nu_{\text{max}}(\text{KBr}/\text{cm}^{-1})$ 3432, 3050, 2955, 2362, 1685, 1476, 1413, 1356 and 1130; δ_{H} (D_2O) 1.21-1.29 (2H, m, CHCH_2CH_2), 1.52-1.62 (2H, apparent quintet, J 7.4, $\text{CHCH}_2\text{CH}_2\text{CH}_2$), 1.66-1.75 (5H, m, CHCH_2 and $\text{CH}=\text{CCH}_3$), 3.48 (1H, t, J 6.6, CHCH_2), 3.61 (2H, t, J 7.0, NCH_2) and 7.33 (1 H, s, $\text{CH}=\text{CCH}_3$); δ_{C} (D_2O) 12.1 ($\text{CH}=\text{CCH}_3$), 22.2 (CHCH_2CH_2), 28.6 ($\text{CHCH}_2\text{CH}_2\text{CH}_2$), 30.9 (CHCH_2), 48.9 (CH_2N), 55.2 (CHCH_2), 111.5 (ArC), 144.0 ($\text{CH}=\text{CCH}_3$), 153.2, 167.9 and 175.6 (CO); m/z 256 (MH^+ , 70%), 212 (100), 197 (30), 183 (34), 169 (60), 146 (28), 127 (28) and 84 (42).

(S)- 2-Amino-5-(N1-uracilyl)pentanoic acid, 3.86



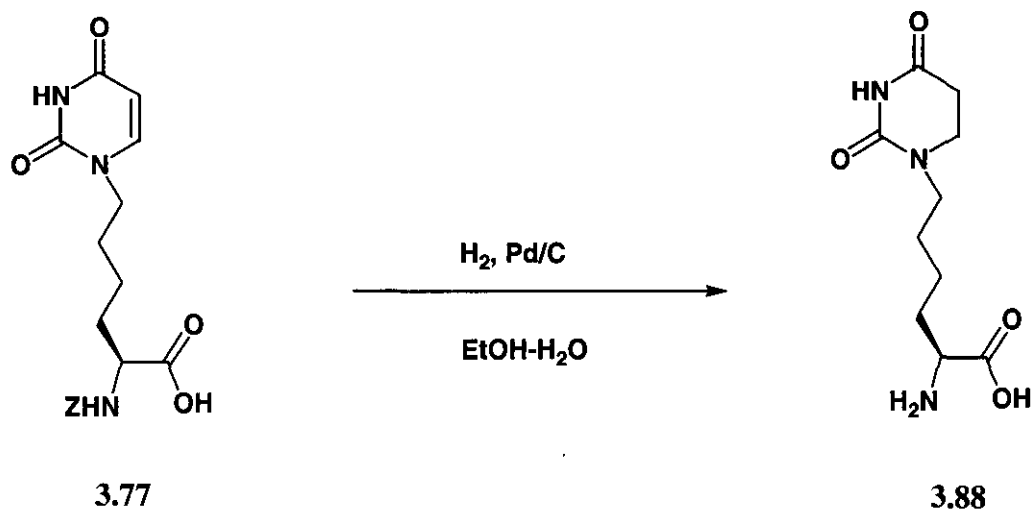
Prepared following method F, using (*S*)-2-benzyloxycarbonylamino-5-(*N*1-uracilyl)pentanoic acid **3.75** (1.23 g, 3.41 mmol) and Pd/C (150 mg) to yield the *title compound* **3.86** as a white solid (580 mg, 75%), m.p. 208-209°C; Found: [M-H]⁻ (ES⁻) 226.0833. C₉H₁₃N₃O₄ requires: M-H 226.0828; ν_{\max} (KBr/cm⁻¹) 3513, 3457, 3090, 1692, 1673, 1609, 1418, 1387, 1249 and 1237; δ_{H} (D₂O) 1.47-1.82 (4H, m, CHCH₂CH₂), 3.59 (1H, t, *J* 5.9, CHCH₂), (2H, m, NCH₂), 5.67 and 7.48 (each 1H, d, *J* 7.8, CH=CH); δ_{C} (D₂O) 24.6 (CHCH₂CH₂), 27.9 (CHCH₂), 48.9 (CH₂N), 54.9 (CHCH₂), 102.2 and 147.8 (CH=CH), 152.9, 167.5 and 174.8 (CO); *m/z* 226 (M-H, 58%), 183 (20), 153 (30), 121 (100), 11 (40) and 90 (60).

(*S*)- 2-Amino-6-(*N*1-uracilyl)hexanoic acid, 3.87



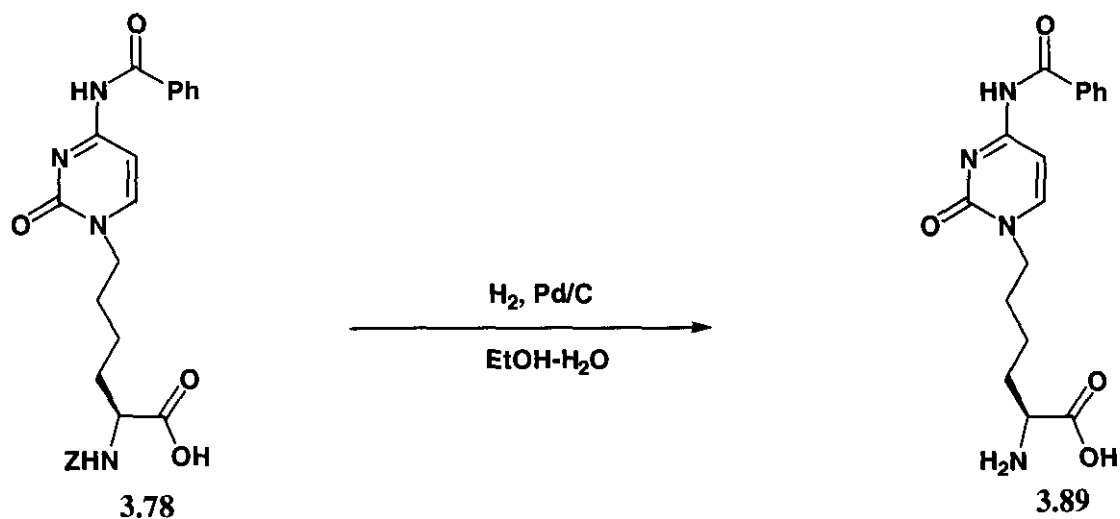
Prepared following method F, using (*S*)-2-benzyloxycarbonylamino-6-(*N*1-uracilyl)hexanoic acid **3.77** (110 mg, 0.293 mmol) and Pd/C (30 mg) for 5 h to yield the *title compound* **3.87** as a white solid (60 mg, 90%), m.p. (decomp.) 187-205°C, that was incompletely characterized; ν_{\max} (KBr/cm⁻¹) 3515, 3460, 3091, 1694, 1675, 1615, 1419, 1389, 1249 and 1235; δ_{H} (D₂O) 1.26-1.93 (6H, m, CHCH₂CH₂CH₂), 3.67 (1H, t, *J* 6.4, CHCH₂), 3.74 (2H, t, *J* 7.3, NCH₂), 5.75 and 7.58 (each 1H, d, *J* 7.8, CH=CH); δ_{C} (D₂O) 22.1 (CHCH₂CH₂), 28.5 (CHCH₂CH₂CH₂), 30.8 (CHCH₂), 49.3 (CH₂N), 55.4 (CHCH₂), 102.3 and 148.1 (CH=CH), 153.2, 167.7 and 175.4 (CO).

(S)-2-Amino-6-(5,6-dihydro-1-uracilyl)hexanoic acid, 3.88



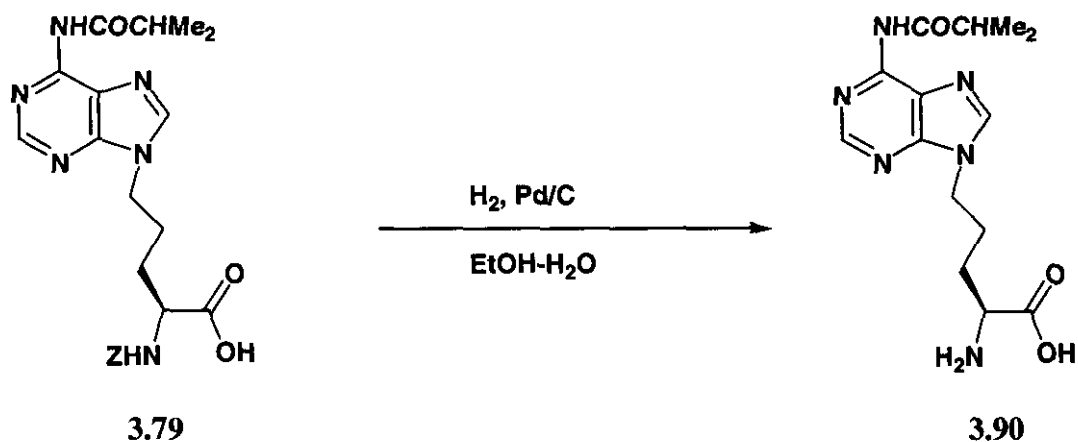
This was prepared following method F, using (S)-2-benzyloxycarbonylamino-6-(N1-uracilyl)hexanoic acid **3.77** (150 mg, 0.40 mmol) and Pd/C (100 mg) but for 16 h to yield the *title compound* **3.88** as a white solid (86 mg, 88%), m.p. (decomp.) 219-220°C; Found: MH^+ (ES^+) 244.1297. $\text{C}_{10}\text{H}_{17}\text{N}_3\text{O}_4$ requires: MH 244.1297; $\nu_{\text{max}}(\text{KBr}/\text{cm}^{-1})$ 3484, 2954, 2931, 2344, 2362, 1729, 1466, 1288, 1275, 1044 and 971; δ_{H} (D_2O) 1.10-1.75 (6H, m, $\text{CHCH}_2\text{CH}_2\text{CH}_2$), 2.63 (2H, t, J 7.2, CH_2CO), 3.22 (2H, t, J 7.3, CH_2N), 3.35 (2H, t, J 7.2, $\text{CH}_2\text{CH}_2\text{CO}$) and 3.94 (1H, m, CHCH_2); δ_{C} (D_2O) 22.5 (CHCH_2CH_2), 27.1 ($\text{CHCH}_2\text{CH}_2\text{CH}_2$), 30.7 (CH_2CO), 31.5 (CHCH_2), 42.5 ($\text{CH}_2\text{CH}_2\text{CO}$), 47.5 (CH_2N), 51.4 (CHCH_2), 148.0, 155.0 and 175.1 (CO); m/z 244 (MH^+ , 18%), 198 (20), 155 (30), 141 (40), 116 (34) and 84 (100). Traces of (S)-2-amino-6-(N1-uracilyl)hexanoic acid **3.87** were also isolated.

(S)-2-Amino-6-(N4-benzoyl-N1-cytosinyl)hexanoic acid, 3.89



This was prepared following method F, using a crude mixture of (S)-6-(N4-benzoyl-N1-cytosinyl)-2-benzyloxycarbonylaminohexanoic acid **3.78** and excess Pd/C (200mg) in EtOH/H₂O 200 ml, 7/3, v/v). The NMR data of the crude sample was complicated and no definite assignment of the peaks could be made, the crude amino acid **3.89** was therefore used in the next step without purification.

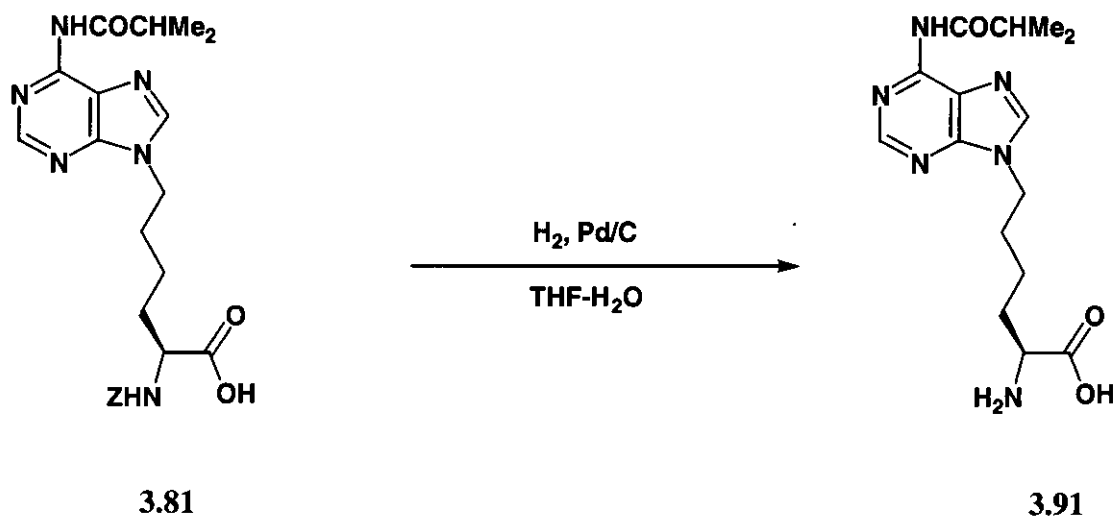
(S)-2-Amino-5-[N6-(2-methylpropanoyl)-N9-adeninyl]pentanoic acid, 3.90



Prepared following method F, using (S)-5-[N6-(2-methylpropanoyl)-N9-adeninyl]-2-benzyloxycarbonylamino-pentanoic acid **3.79** (190 mg, 0.419 mmol) and Pd/C (200 mg) to yield the *title compound* **3.90** as a white solid (100 mg, 75%), m.p. (decomp) 110-112°C; Found: MH⁺ (ES⁺) 321.1680. C₁₄H₂₀N₆O₃ requires: MH 321.1675; ν_{max} (KBr/cm⁻¹) 3386, 2971, 2934, 2377, 1794, 1774, 1611, 1459, 1219 and 966; δ_{H} (D₂O) 1.13 (6H, d, *J* 7.0,

CHMe₂), 1.58 (2H, m, CHCH₂CH₂), 1.77 (2H, m, CHCH₂), 2.75 (1H, septet, *J* 7.0, CHMe₂), 3.35 (1H, m, CHCH₂), 4.22 (2H, m, NCH₂), 8.27 and 8.53 (each 1H, s, 2-CH and 8-CH); δ_C (CD₃OD) 26.9 (CHCH₂CH₂), 29.3 (CHCH₂), 37.1 (CHMe₂), 44.65 (NCH₂), 49.0 (CHCH₂), 124.5 (ArC), 128.8 and 129.4 (ArCH), 145.7 and 151.0 (ArC), 153.0 and 178.0 (CO); *m/z* 321 (MH⁺, 35%), 206 (30), 165 (55), 152 (65), 133 (64) and 115 (72).

(S)-2-Amino-6-[N6-(2-methylpropanoyl)-N9-adeninyl]hexanoic acid, 3.91

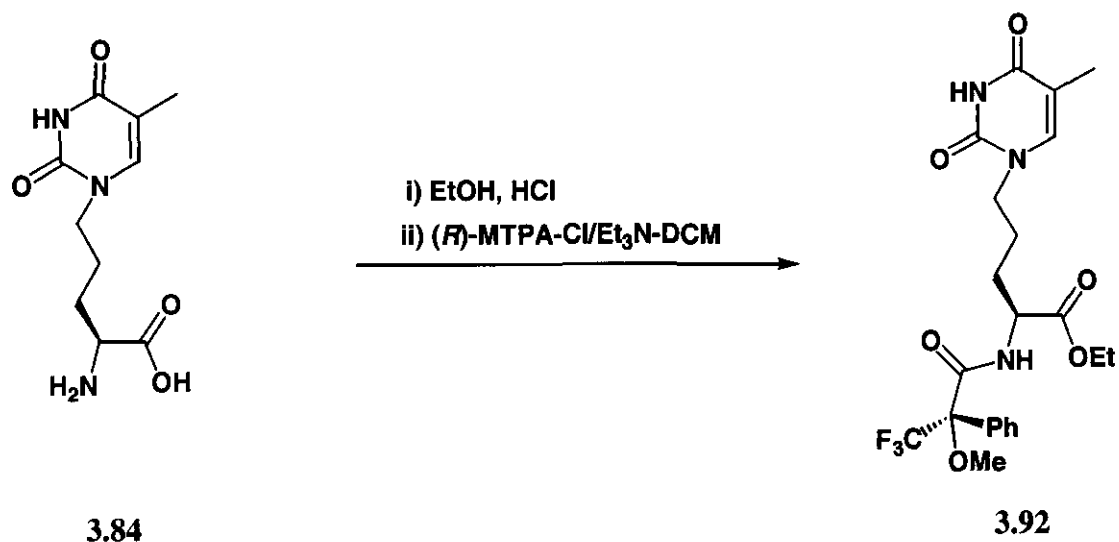


Prepared following method F, using (S)-2-benzyloxycarbonylamino-6-[N6-(2-methylpropanoyl)-N9-adeninyl]hexanoic acid **3.81** (230 mg, 0.491 mmol) and Pd/C (200 mg) to yield the *title compound* **3.91** as a white hygroscopic solid (100 mg, 61%); Found: MH⁺ (ES⁺) 335.1824. C₁₅H₂₂N₆O₃ requires: MH 335.1831; δ_H (D₂O) 0.60 (6H, d, *J* 6.9, CHMe₂), 1.28 (2H, m, CHCH₂CH₂), 1.06-1.31 (4H, m, CHCH₂ and NCH₂CH₂), 2.20 (1H, septet, *J* 6.9, CHMe₂), 3.07 (1H, t, *J* 5.9, CHCH₂), 3.61 (2H, t, *J* 7.2, NCH₂), 7.66 and 7.87 (each 1H, s, 2-CH and 8-CH); δ_C (D₂O) 19.25 (CHCH₂CH₂), 22.4 (NCH₂CH₂CH₂), 30.7 (CHCH₂), 36.7 (CHMe₂), 44.5 (NCH₂), 55.3 (CHCH₂), 123.6 (ArC), 146.1 (ArCH), 149.2 (ArC), 152.0 (ArCH) 152.2 (ArC), 176.5 and 181.2 (CO); *m/z* 335 (MH⁺, 80%), 291 (80), 265 (100), 221 (90), 204 (60), 178 (100), 149 (40) and 136 (80).

General method for conversion of an amino acid into its (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (Mosher amide) (method G)

Acetyl chloride (10 mol equiv.) was added dropwise at 0°C to the amino acid (~50 mg) stirred in ethanol (~40 ml). The mixture was then stirred overnight at 25°C, heated at reflux for 4 h, cooled and the solvent evaporated under reduced pressure to give the ethyl ester hydrochloride salt which was further dried under vacuum overnight. (*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl chloride (MTPA-Cl) was added dropwise at room temperature to the ester hydrochloride stirred in dichloromethane (4 cm³) and triethylamine (4 cm³). The mixture was stirred overnight then water (20 cm³) was added and the mixture extracted with ethyl acetate (3 x 20 cm³). The combined ethyl acetate layers were washed with saturated sodium hydrogen carbonate solution (3 x 10 cm³), dried (MgSO₄) and evaporated under reduced pressure. The crude material was purified by column chromatography (ethyl acetate/hexane, 50/50) to yield the desired Mosher amide.

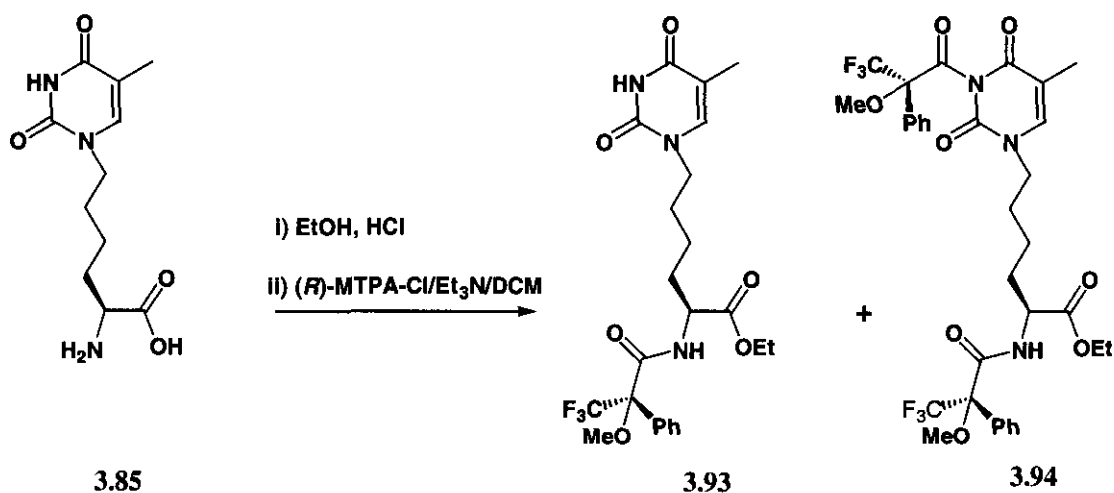
Ethyl (*S*)-2-amino-5-(*N*1-thyminyl)pentanoate (*S*)-MTPA amide, **3.92**



Prepared following method G from amino acid **3.84** to yield the *title compound* **3.92** as a colourless oil; Found: MH⁺ (ES⁺) 486.1856. C₂₂H₂₆F₃N₃O₆ requires: MH 486.1852; δ_H major and minor* diastereoisomers: 1.30 and 1.26* (3H, t, *J* 7.1, CH₂CH₃), 1.53-1.96 (7H, m, CHCH₂CH₂ and CH=CCH₃), 3.45 and 3.35* (3 H, s, OCH₃), 3.56-3.78 (2H, m, NCH₂), 4.24 (2H, q, *J* 7.1, CH₂CH₃), 4.66 (1H, dt, *J* 4.6 and 8.3, CHCH₂), 6.85 and

7.05* (1H, s, CH=CCH₃), 7.35-7.44 (4H, m, NHCH and ArH), 7.54-7.57 (2H, m, ArH), 9.04 and 9.00* (1H, s, ArNH); δ_{C} 12.3 (CH=CCH₃), 14.1 (CH₂CH₃), 24.9 (CHCH₂CH₂), 29.5 (CHCH₂CH₂), 47.4 (NCH₂), 51.1 (CHCH₂), 55.3 (OCH₃), 62.1 (CH₂CH₃), 83.7 (CF₃), 110.8 (CH=CCH₃), 125.4 (quaternary C), 127.2, 128.6 and 129.6 (ArCH), 132.8 (ArC), 140.2 (CH=CCH₃), 150.8, 164.2, 166.7 and 171.2 (CO); m/z 486 (M⁺, 10%), 296 (100), 268 (20), 222 (90), 189 (70) and 105 (80); δ_{F} (minor diastereoisomer) -69.074, (major diastereoisomer) -68.790, e.e: 85%.

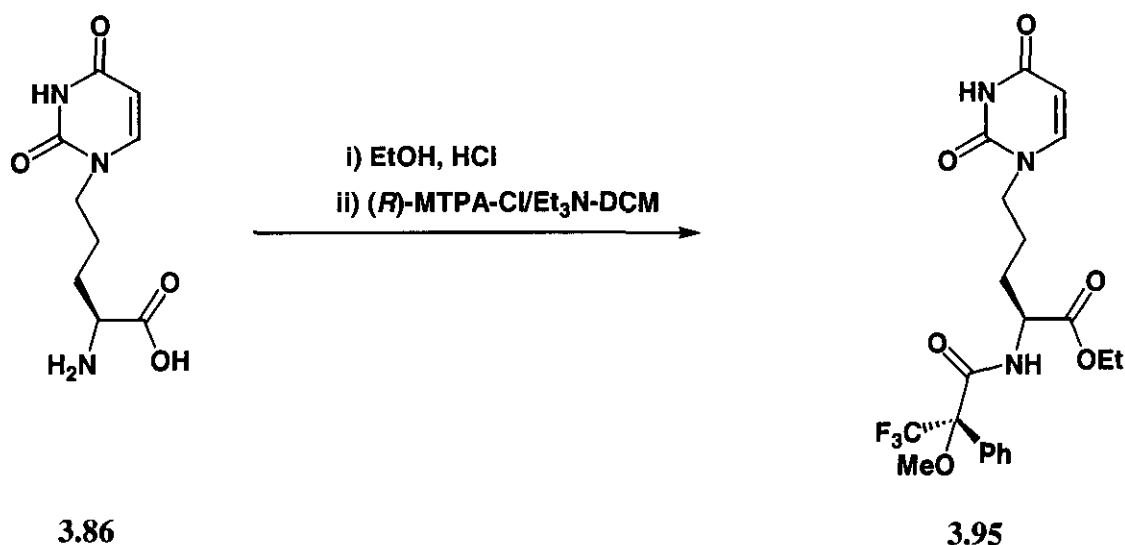
Ethyl (S)-2-Amino-6-(N1-thyminy)hexanoate (S)-MTPA amide, 3.93 and ethyl (S)-2-amino-6-(N1-thyminy)hexanoate (S)-MTPA diamide, 3.94



Prepared following method G from amino acid **3.85** to yield the *title monoamide* **3.93** and the *title diamide* **3.94**, both as colourless oils. Ethyl (S)-2-Amino-6-(N1-thyminy)hexanoate (S)-MTPA amide **3.93**: Found: MH⁺ (ES⁺) 500.2019. C₂₃H₂₈F₃N₃O₆ requires: MH 500.2008; δ_{H} major and minor* diastereoisomers: 1.28 and 1.21* (3H, t, *J* 7.2, CH₂CH₃), 1.59-1.97 (9H, m, CHCH₂CH₂CH₂ and CH=CCH₃), 3.34* and 3.54 (3H, s, OCH₃), 3.61 (2H, t, *J* 6.8, NCH₂), 4.16 (2H, q, *J* 7.2, CH₂CH₃), 4.56 (1H, dt, *J* 5.1 and 8.2, CHCH₂), 6.89 and 6.98* (1H, s, CH=CCH₃), 7.10 (1H, d, *J* 8.2, NHCH), 7.31-7.36 (3H, m, ArH), 7.61-7.63 (2H, m, ArH) and 8.51 (1H, s, imide NH); δ_{C} 12.3 (CH=CCH₃), 14.1 (CH₂CH₃), 22.1, 28.3 and 31.6 (CH₂), 47.8 (NCH₂), 51.7 (CHCH₂), 55.3 (OCH₃), 61.84 (CH₂CH₃), 84.0 (CF₃), 110.8 (CH=CCH₃), 125.4 (quaternary C), 127.2, 128.5 and

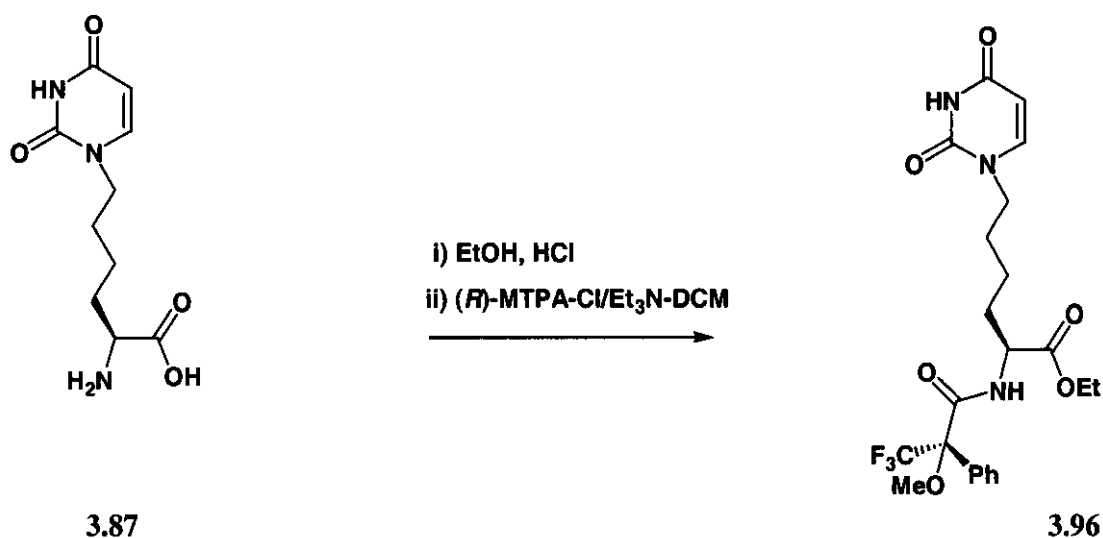
129.6 (ArCH), 133.0 (ArC), 140.1 (CH=CCH₃), 150.7, 163.9, 166.45 and 171.5 (CO); *m/z* 499 (M⁺, 100%), 426 (70) 374 (30), 354 (20), 338 (40) and 324 (28). δ_F minor diastereoisomer -69.325 , major diastereoisomer -68.869 , e.e: 88%. Ethyl (2*S*)-amino-6-(1-thyminy)hexanoate (*S*)-MTPA diamide **3.94**: Found: MNH₄⁺ (ES⁺) 733.2668. C₃₃H₃₅F₆N₃O₈ requires: MNH₄ 733.2672; δ_H major and minor* diastereoisomers: 1.26 and 1.22* (3H, t, *J* 7.2, CH₂CH₃), 1.61-1.94 (9H, m, CHCH₂CH₂CH₂ and CH=CCH₃), 3.34* and 3.45 and 3.49 (6H, s, 2 x OCH₃), 3.61 (2H, t, *J* 6.8, NCH₂), 4.21 (2H, q, *J* 7.2, CH₂CH₃), 4.62 (1H, dt, *J* 5.1 and 8.2, CHCH₂), 6.91 and 6.99* (1H, s, CH=CCH₃), 7.17 (1H, d, *J* 8.2, NHCH), 7.26-7.45 (6H, m, ArH), 7.54-7.57 (2H, m, ArH) and 7.68-7.71 (2H, m, ArH); δ_C 12.3 (CH=CCH₃), 14.1 (CH₂CH₃), 22.1, 28.2 and 31.85 (CH₂), 48.4 (NCH₂), 51.6 (CHCH₂), 54.7 and 55.3 (OCH₃), 61.9 (CH₂CH₃), 84.0 (CF₃), 110.55 (CH=CCH₃), 121.6 (CF₃), 124.8 and 125.4 (quaternary C), 127.3, 128.3, 128.5, 128.6, 128.7 and 129.65 (ArCH), 131.2 and 132.8 (ArC), 139.9 (CH=CCH₃), 149.2, 162.6, 166.4, 171.5 and 171.9 (CO); *m/z* 716 (M⁺, 16%), 517 (100), 500(80), 468 (50), 391 (20), 337 (65) and 286 (70). δ_F (minor diastereoisomer) -69.206 and -70.136 , (major diastereoisomer) -68.830 and -70.017 , e.e: 88%.

Ethyl (*S*)-2-amino-5-(*N*1-uracilyl)pentanoate (*S*)-MTPA amide, **3.95**



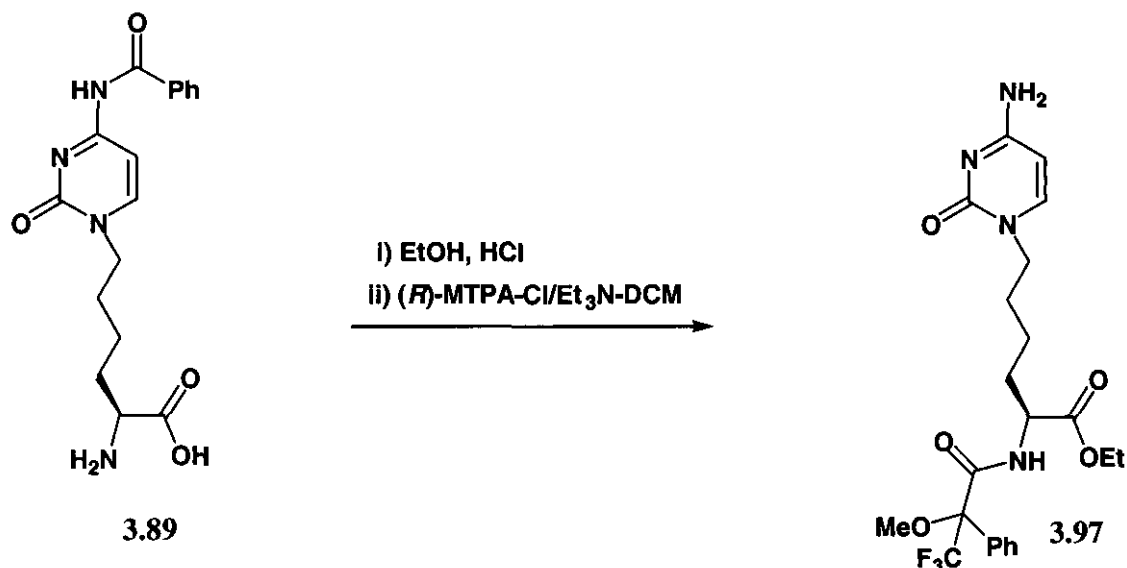
Prepared following method G from **3.86** to yield the *title compound* **3.95** as a colourless oil; Found: MNH_4^+ (ES^+) 489.1959. $\text{C}_{21}\text{H}_{24}\text{F}_3\text{N}_3\text{O}_6$ requires: MNH_4 489.1961; δ_{H} major and minor* diastereoisomer: 1.30 and 1.26* (3H, t, J 7.1, CH_2CH_3), 1.50-1.96 (4H, m, CHCH_2CH_2), 3.45 and 3.34* (3H, s, OCH_3), 3.48-3.77 (2H, m, NCH_2), 4.23 (2H, q, J 7.1, CH_2CH_3), 4.67 (1H, m, CHCH_2), 5.54 and 5.69* (1H, d, J 1.8 and 7.8 or 7.9*, $\text{CH}=\text{CHCO}$), 6.92 and 7.21* (1H, J 7.8 and 7.9*, $\text{CH}=\text{CHCO}$), 7.34-7.59 (5H, m, ArH) and 9.38 (1H, s, imide NH); δ_{C} 14.1 (CH_2CH_3), 24.6 (CHCH_2CH_2), 29.5 (CHCH_2), 47.9 (NCH_2), 50.85 (CHCH_2), 55.2 (OCH_3), 62.2 (CH_2CH_3), 84.0 (CF_3) 101.9 ($\text{CH}=\text{CHCO}$), 121.6 (quaternary C), 128.55, 128.7 and 129.5 (ArCH), 132.6 (ArC), 143.9 ($\text{CH}=\text{CHCO}$), 149.1, 161.7, 166.8 and 171.1 (CO); m/z 472 (MH^+ , 65%), 398 (100), 346 (80) and 296 (28); δ_{F} (minor diastereoisomer) -68.444 , (major diastereoisomer) -68.157 , e.e: 88%.

Ethyl (*S*)-2-Amino-6-(*N*1-uracilyl)hexanoate (*S*)-MTPA amide **3.96**



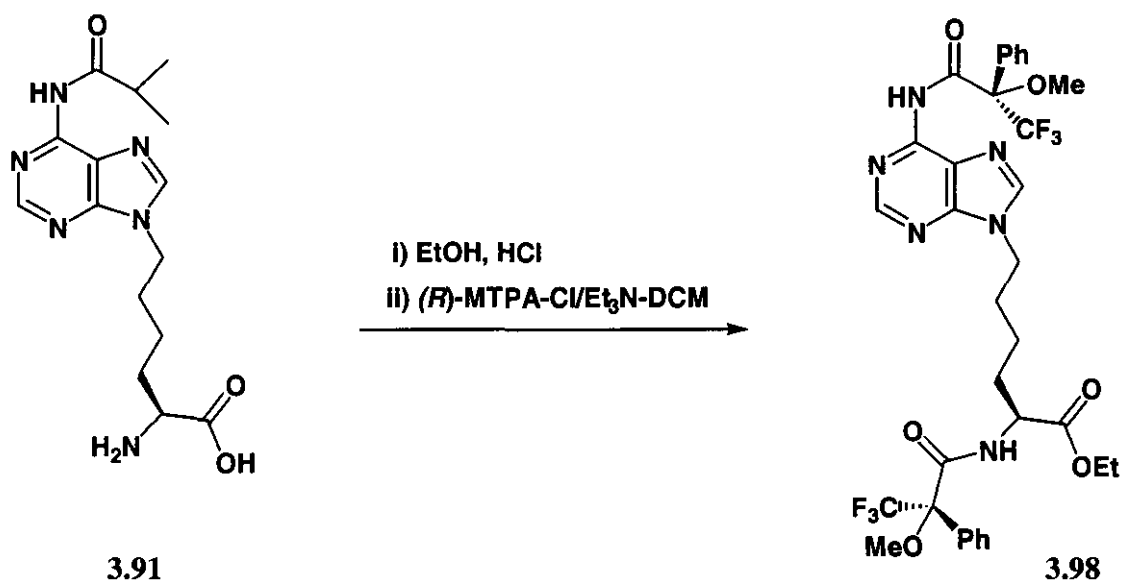
Prepared following method G from amino acid **3.87** to yield the *title compound* **3.96** as a colourless oil, incompletely characterized; Found: MNH_4^+ 491.2117. $\text{C}_{21}\text{H}_{24}\text{N}_3\text{O}_6\text{F}_3$ requires: MNH_4 491.2111; δ_{F} (minor diastereoisomer) -69.134 , (major diastereoisomer) -68.869 , e.e: 89%.

Ethyl (S)-2-amino-6-(N4-benzoyl-N1-cytosinyl)hexanoate ester MTPA amide, 3.97



This was prepared following method G using crude (S)-2-amino-6-(N4-benzoyl-N1-cytosinyl)hexanoic acid to give ethyl (S)-2-amino-6-(N4-benzoyl-N1-cytosinyl)hexanoate ester MTPA amide which was directly analysed by ¹⁹F NMR. δ_F (major diastereoisomer) – 68.830; (minor diastereoisomer) –69.369; e.e. 81%.

Ethyl (S)-2-amino-6-(N9-adeninyl)hexanoate (S)-MTPA diamide, 3.98



Prepared following method G from **3.91** to give the *title compound* **3.98**; Found: MH⁺ (ES⁺) 725.2516. C₃₃H₃₄N₆O₆F₆ requires: MH 725.2522; δ_H minor* and major

diastereoisomers: 1.26* and 1.29 (3H, t, J 7.2, CH_2CH_3), 1.58-1.91 (6H, m, $\text{CHCH}_2\text{CH}_2\text{CH}_2$), 3.32* and 3.46 (3H, s, OCH_3), 3.47 and 3.52* (3H, s, OCH_3), 3.76 (2H, m, NCH_2), 4.22 (2H, q, J 7.2, CH_2CH_3), 4.58 (1H, dt, J 5.3 and 8.2, NHCHCH_2), 7.13 (1H, d, J 8.2, CONHCH), 7.37-7.67 (10H, m, ArH), 7.92 and 8.00* (1H, s, ArH), 8.78 and 8.80* (1H, s, ArH) and 9.60 (1H, s, CONH); δ_{C} 14.2 (CH_2CH_3), 22.4, 29.3 and 31.7 (CH_2), 47.7 (NCH_2), 51.6 (CHCH_2), 55.3 and 55.6 (OCH_3), 110.6 and 113.3 (quaternary C), 84.4 (CF_3) 122.8 (ArC), 127.2, 127.7, 128.4, 128.5 and 128.75 (ArCH), 129.0 (CF_3), 129.6 (ArCH), 131.7 and 132.9 (ArC), 143.1 (ArCH), 148.2 and 152.2 (ArC), 152.5 (ArCH), 163.7, 166.4 and 171.4 (CO); m/z 725 (MH^+ , 100%), 535 (5), 189 (20) and 105 (8); δ_{F} major diastereoisomer -68.871 and -69.423; minor diastereoisomer -69.181 and -69.277; e.e. 86%.

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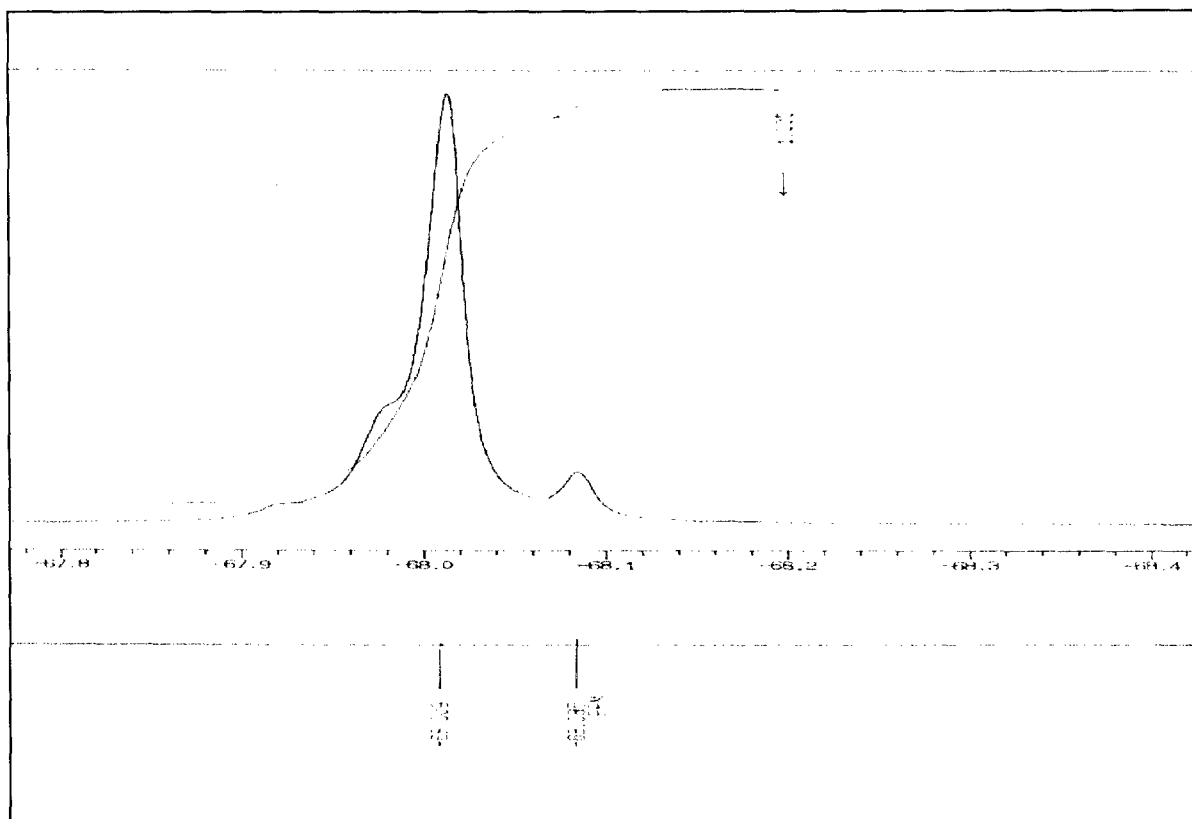
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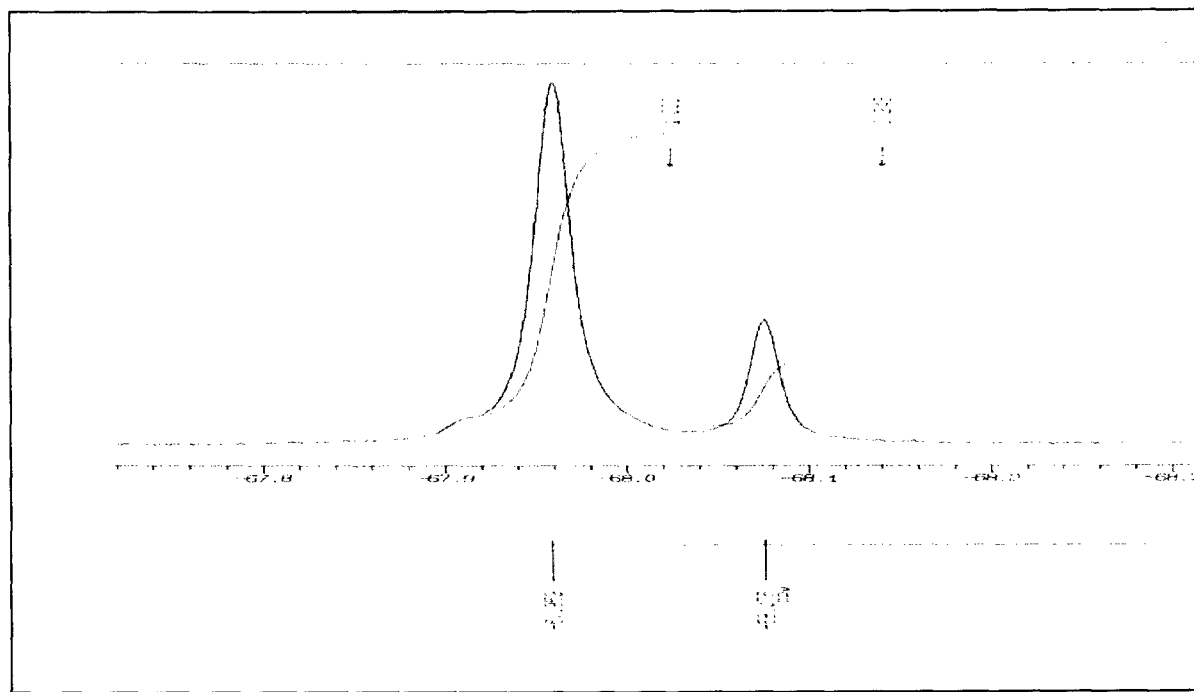
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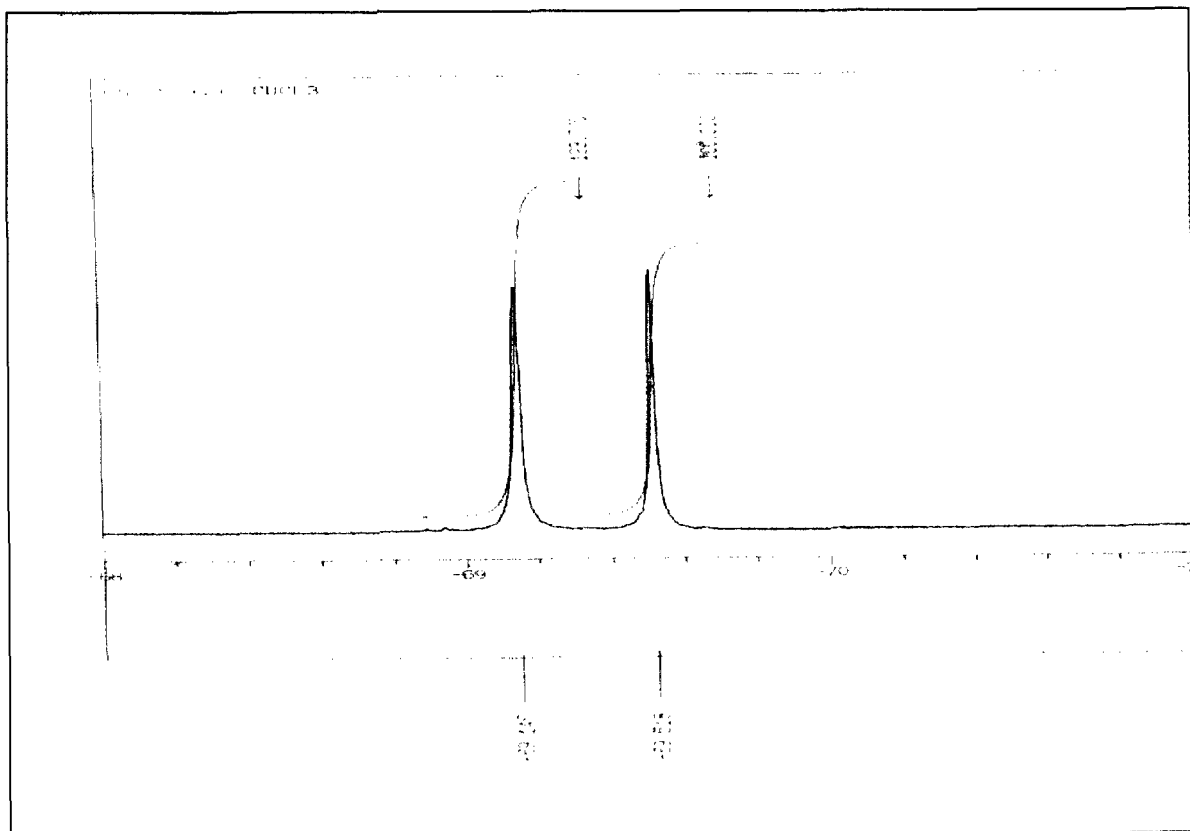
Appendix



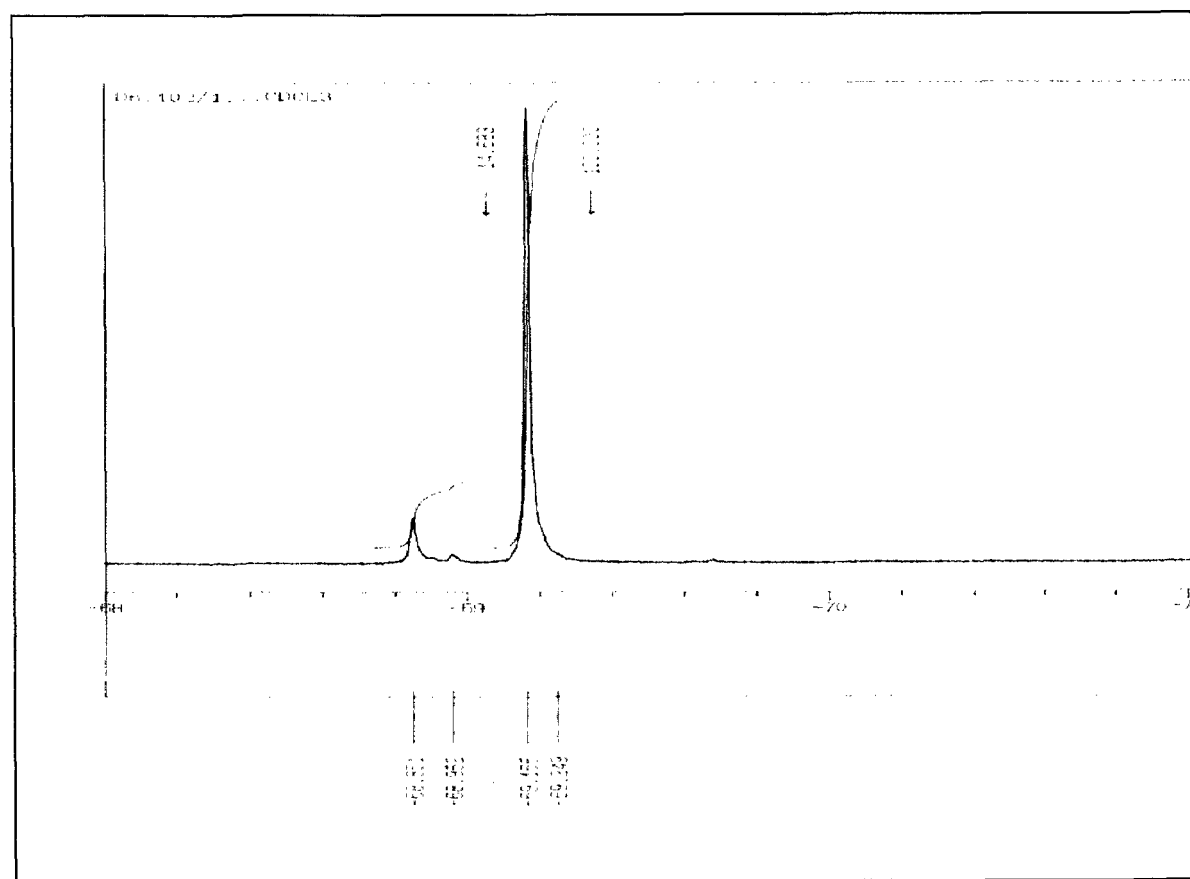
^{19}F NMR of Mosher amide 2.81



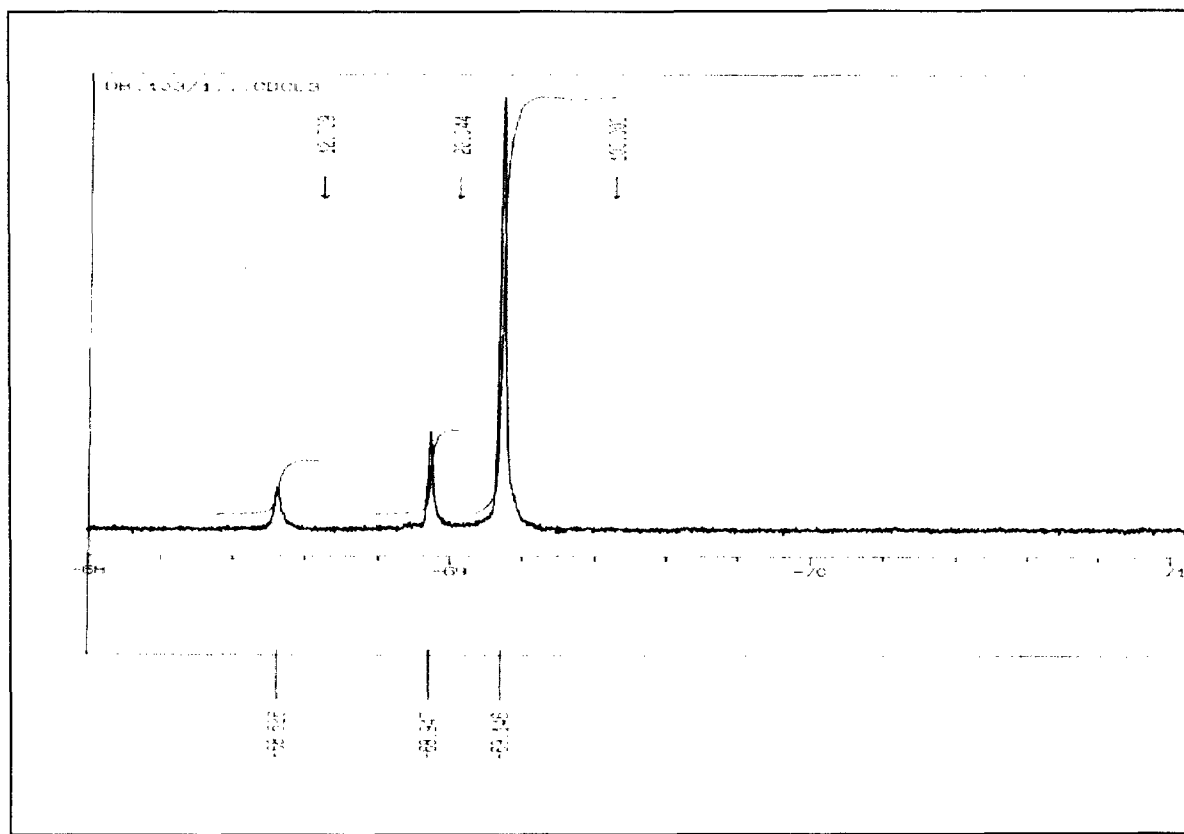
^{19}F NMR of Mosher amide 2.82



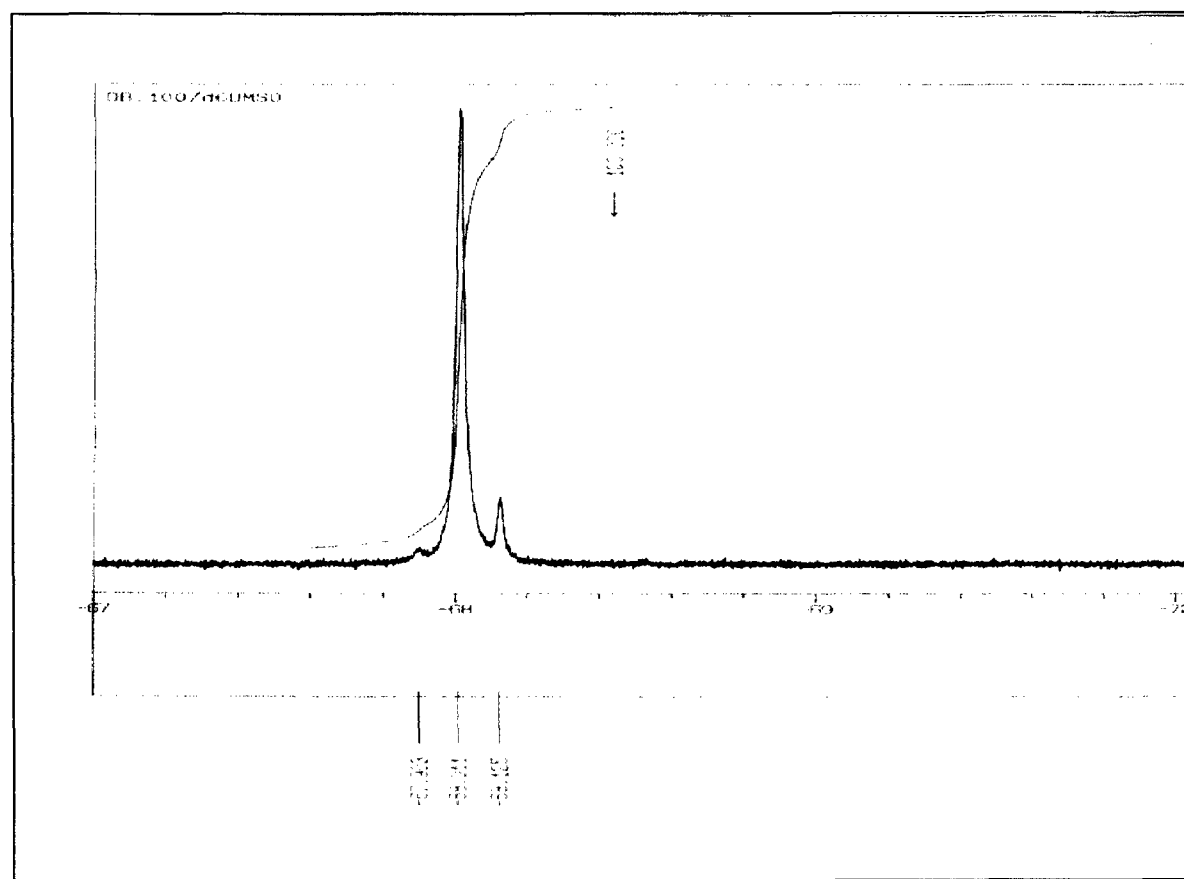
¹⁹F NMR of Mosher amide 2.83



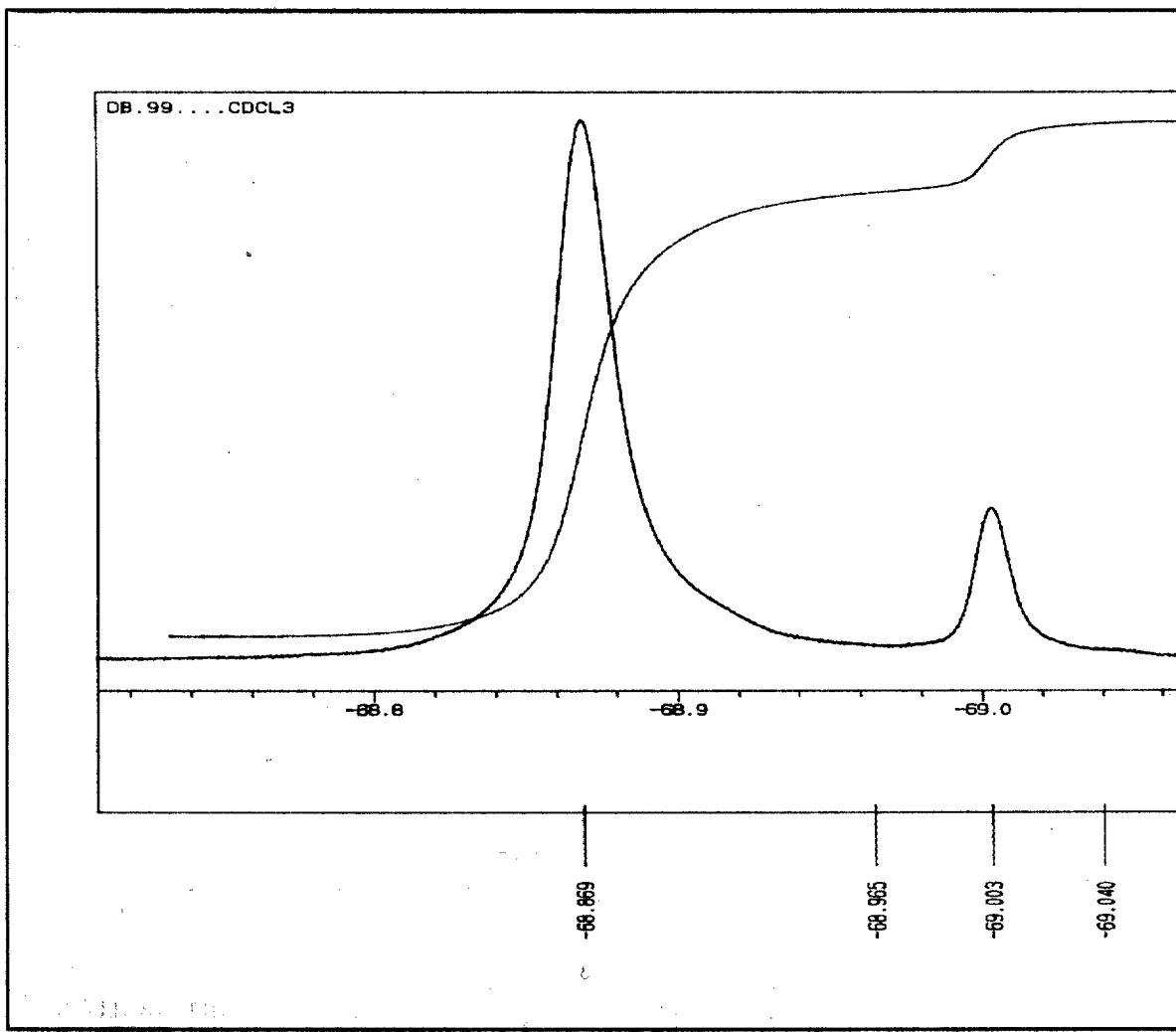
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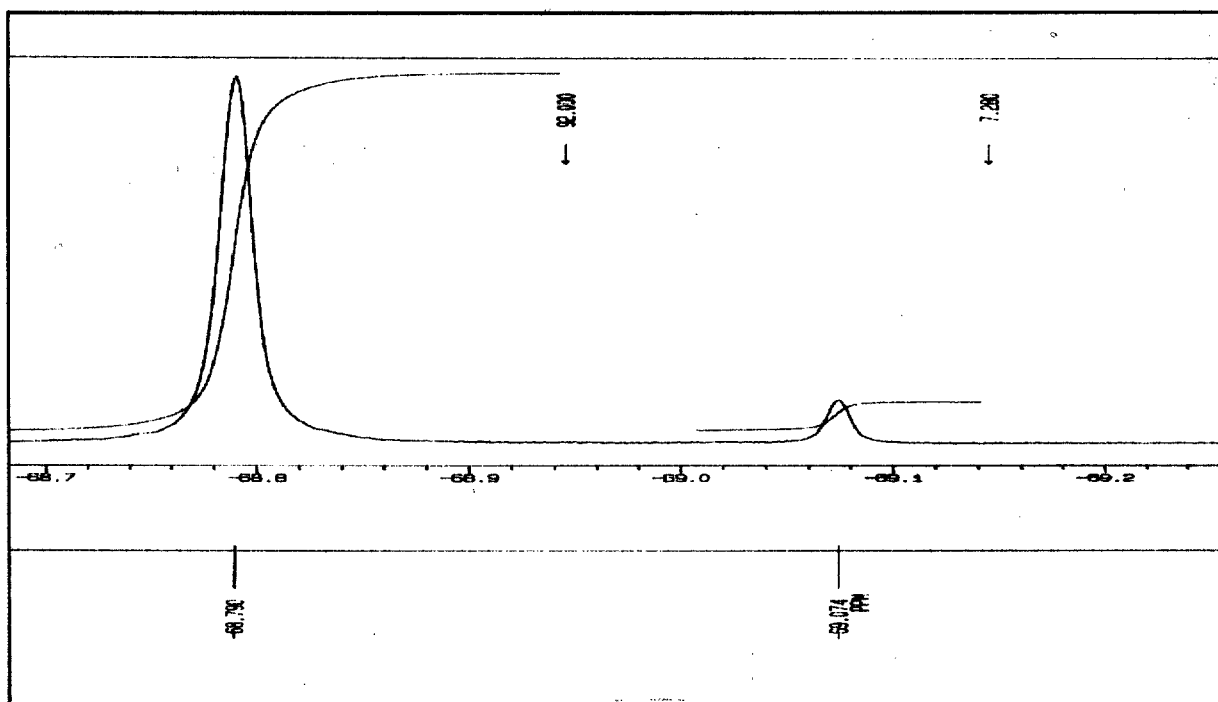
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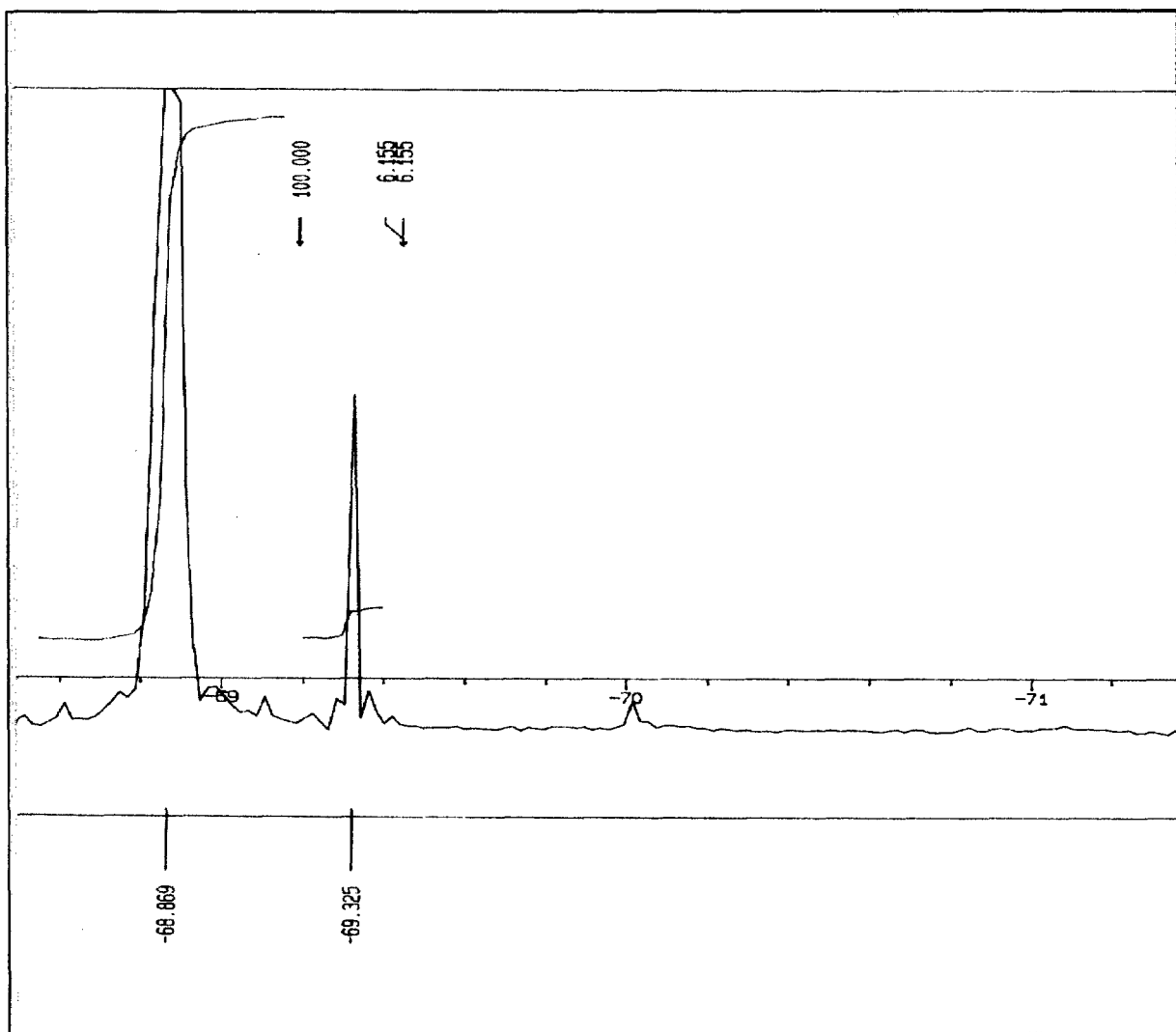
¹⁹F NMR of Mosher amide 2.86



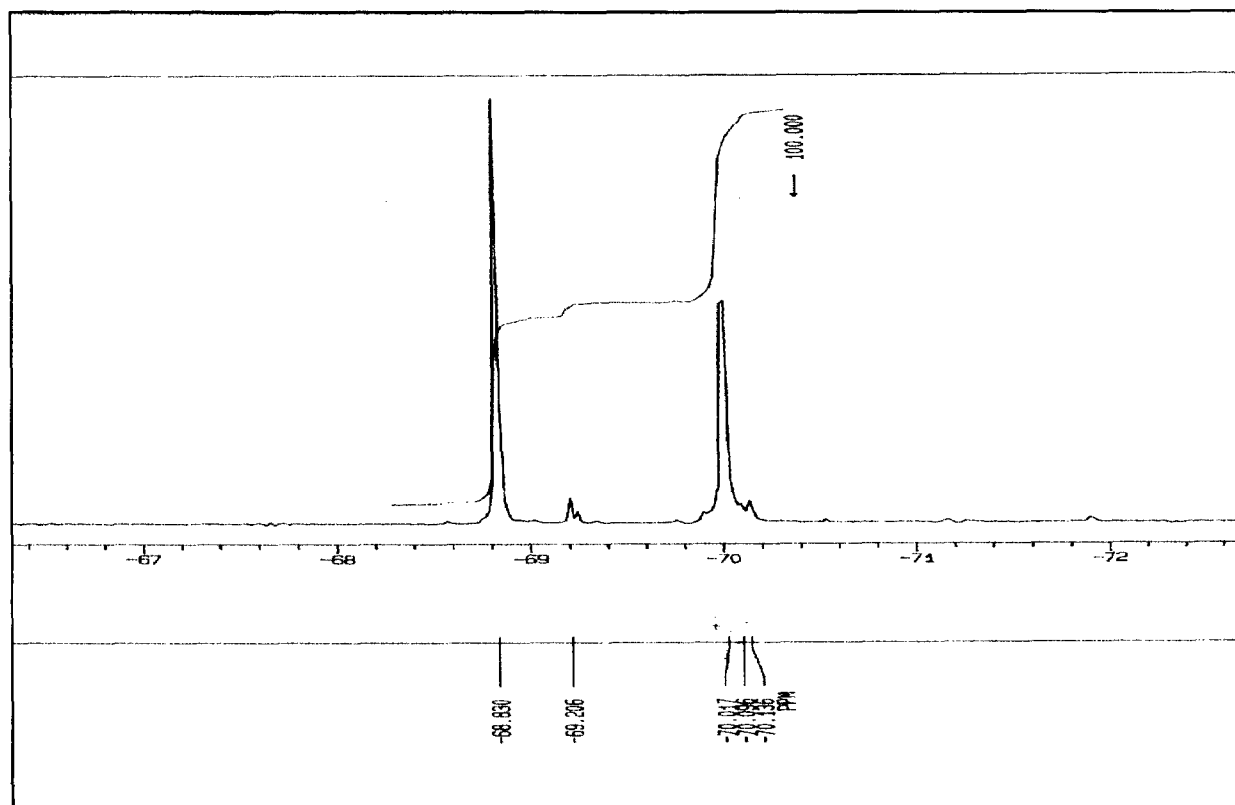
^{19}F NMR of Mosher amide 2.87



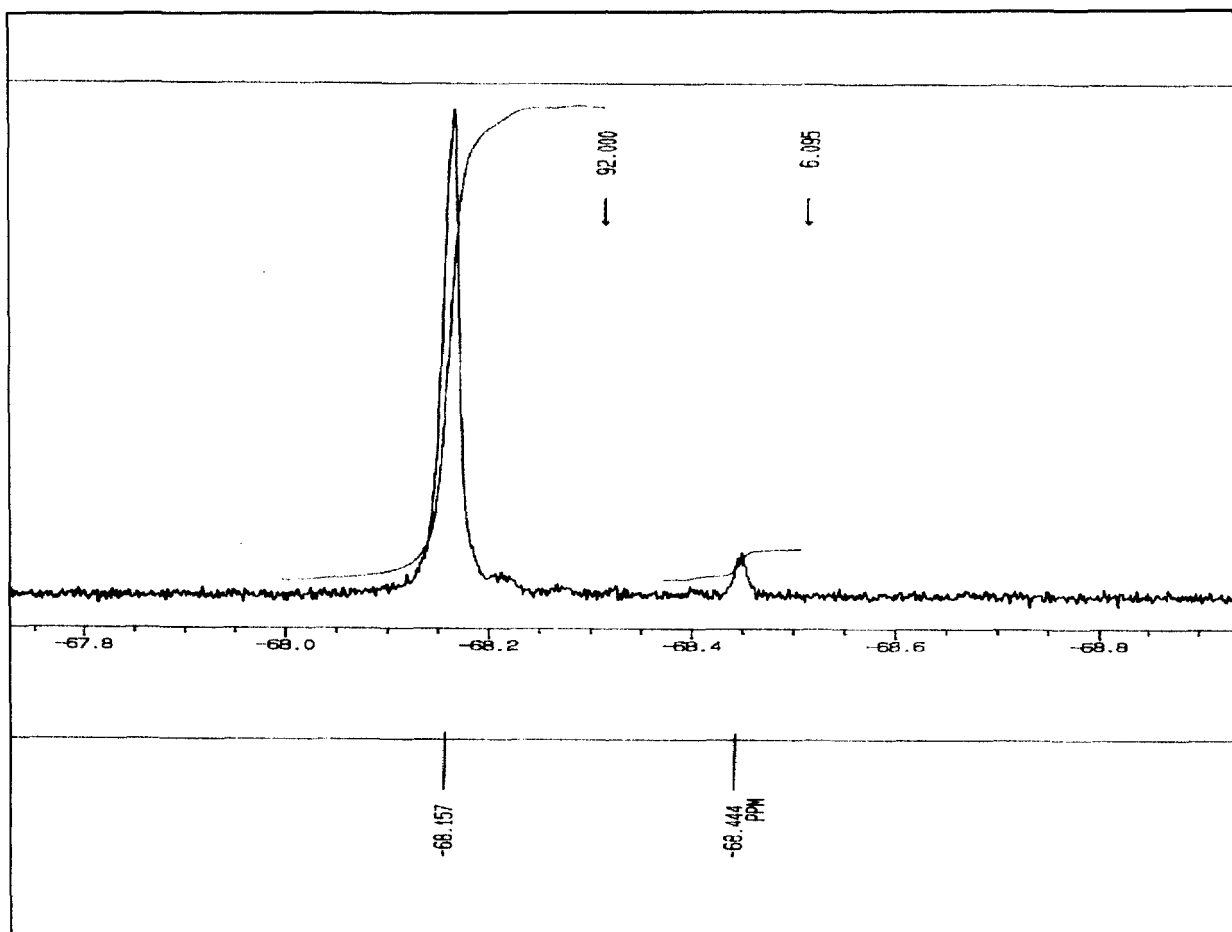
^{19}F NMR of ethyl (*S*)-2-amino-5-(1-thyminyl)pentanoate (*S*)-MTPA amide, 3.92



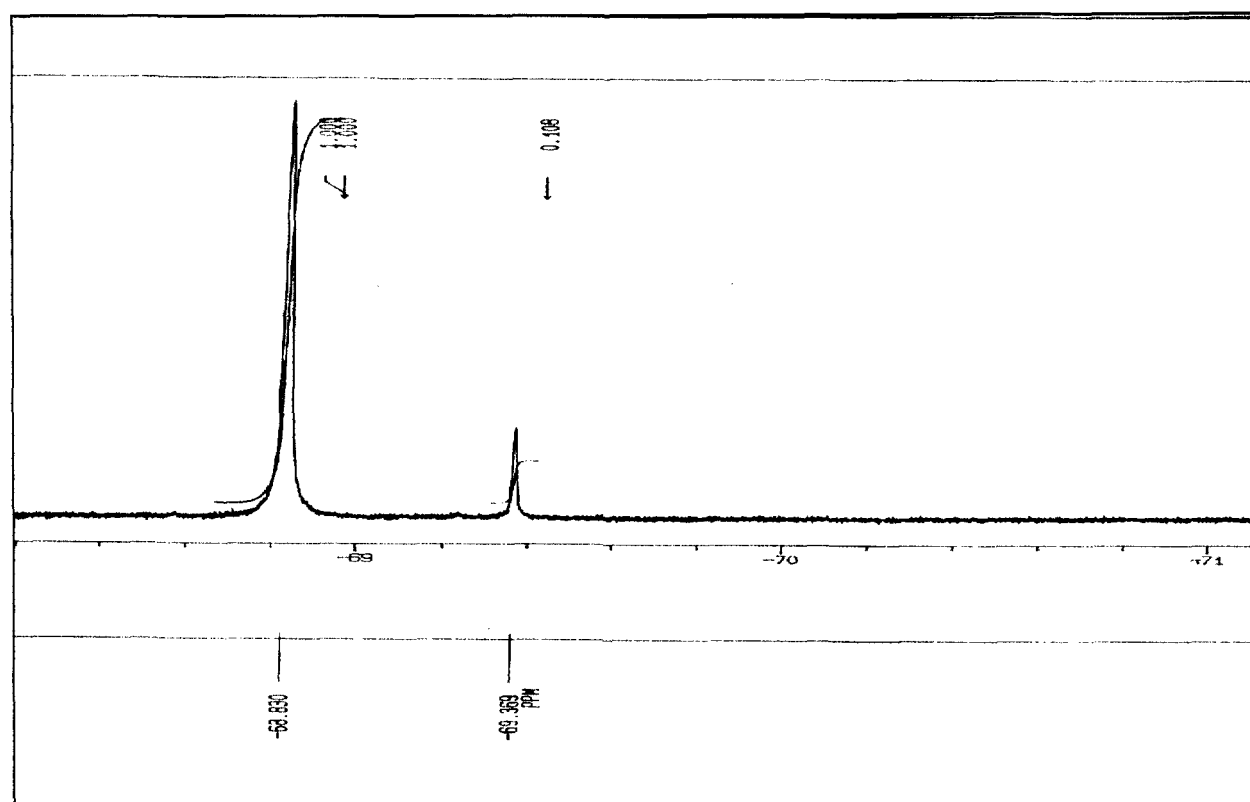
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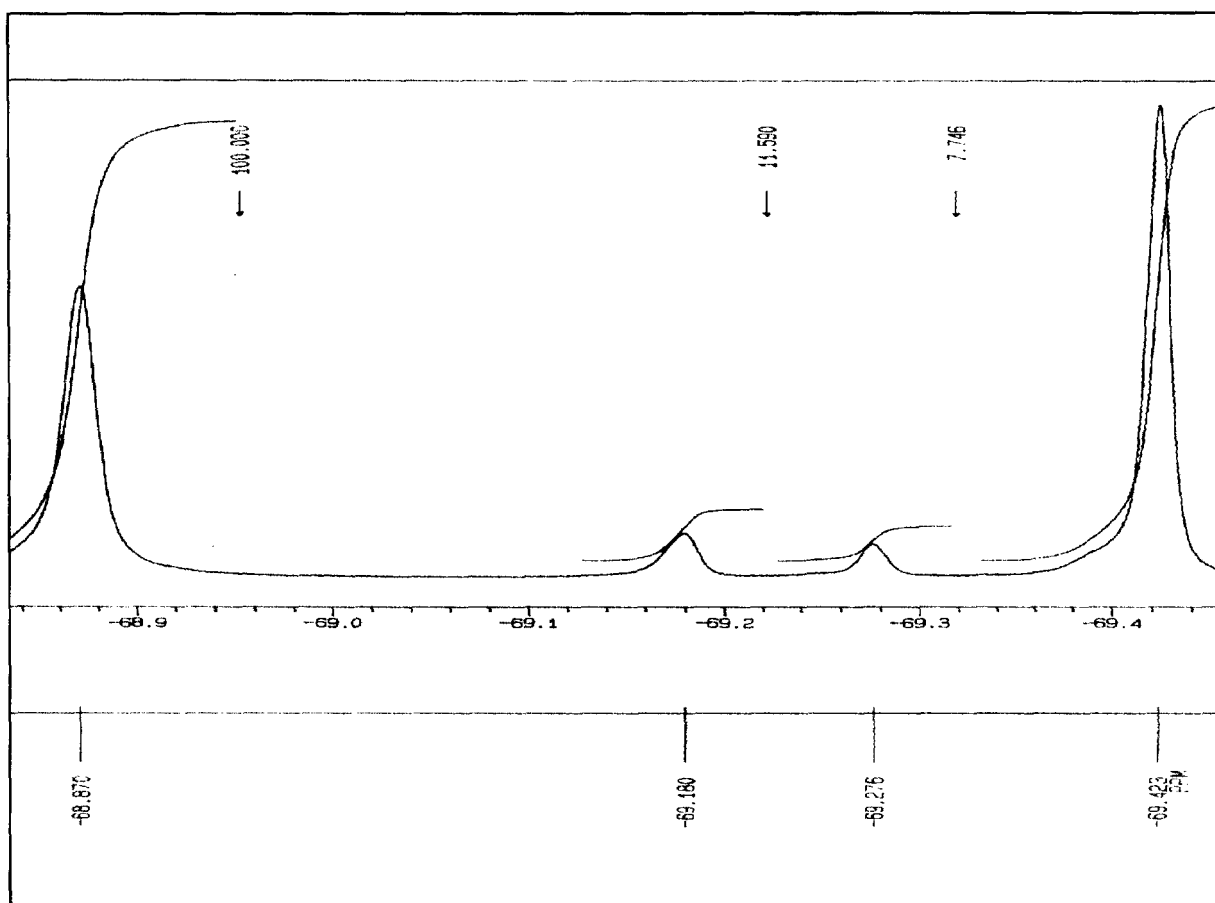
¹⁹F NMR of ethyl (*S*)-2-amino-6-(1-thyminy)hexanoate (*S*)-MTPA diamide, 3.94



¹⁹F NMR of ethyl (*S*)-2-amino-5-(1-uracilyl)pentanoate (*S*)-MTPA amide, 3.95



¹⁹F NMR of ethyl (*S*)-2-amino-6-(*N*⁴-benzoyl-1-cytosinyl)hexanoate ester MTPA amide, 3.97



^{19}F NMR of ethyl (*S*)-2-amino-6-(9-adeninyl)hexanoate (*S*)-MTPA diamide, 3.98